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Doutoramento em Química
(Química Orgânica)

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Amélia Pilar Rauter, Professora Associada com Agregação
Yves Queneau, Directeur de Recherche au CNRS

2010

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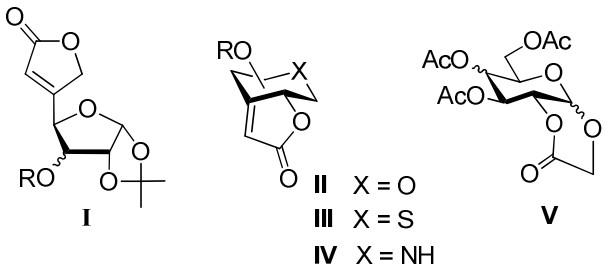
Abstract

This PhD research work was focused on the synthesis and uses of bicyclic carbohydrate lactones, in the context of the access to new sugar derivatives containing an α,β-unsaturated carbonyl function. These molecular targets, chosen for the intrinsic bioactivity associated to the conjugated carbonyl system, were synthesized and submitted to biological evaluation, particularly their effect towards fungi and bacteria. Moreover, the inclusion of conjugated carbonyl systems in carbohydrates provides suitable templates for further derivatization, to which a variety of reactions may be applied. Three types of bicyclic sugar lactones were investigated: furanose C-C-linked butenolides (compounds type **I**), pyranose-fused butenolides, including *S*- or *NH*-analogues (compounds type **II**–**IV**), and carboxymethyl glycoside-derived lactones (CMGLs, compounds type **V**).

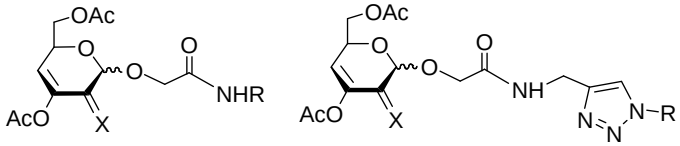


I **V**

The access to butenolide containing-sugars was explored. The synthetic methodology was based on the Wittig olefination of easily prepared 3- or 5-keto sugars and spontaneous intramolecular lactonization of the intermediate γ-hydroxy α,β-unsaturated esters. In the case of the bicyclic fused derivatives, furanos-3-uloses containing acid labile 5-*O* or 5,6-di-*O*-protecting groups were used as precursors and converted into the corresponding (*Z*)- or (*E*)-3-*C*-(ethoxycarbonyl)methylene furanoses. Further acid-mediated hydrolysis made possible their isomerization to the pyranose ring and concomitant intramolecular transesterification leading directly to the target compounds in good overall yields. Such bicyclic systems featured the butenolide moiety annelated at C-2-C-3 (compounds type **II**) or at C-3-C-4 of the sugar backbone, depending on the stereochemistry of the C3-C3'double bond. The introduction of a sulfur function at C-5 of the furanoid 3-*C*-α,β-unsaturated esters, widened the scope of this methodology to thiosugar analogues of type **III**. When this approach was applied to related 5-azido

furanoid esters aiming at imino sugar-based molecules of type **IV**, different carbohydrate derivatives comprising both an amide functionality and an α,β-unsaturated carbonyl system were obtained. The (*E*)- and (*Z*)-3-*C*-(ethoxycarbonyl)methylene 5-amino furanoses were converted to a furanose-fused α,β-unsaturated δ-lactam and to a butenolide-containing *N*-ethylformamide, respectively. Moreover, the hydrolysis of the 1,2-*O*-isopropylidene group of the (*Z*)-5-azido furanose precursor, followed by azide reduction, provided a 2-keto iminopyranose, which led to the 1,2-dihydropyridin-3-one system upon acetylation.

CMGLs (compounds type **V**) were used as precursors for 3-enopyranosid-2-uloses (compounds type **VI**). The opening of the lactone moiety by amines provided tri-*O*-acylated 2-hydroxy pyranosides which by oxidation/elimination generated the enone system. Further Wittig olefination afforded 2-*C*-branched-chain conjugated dienepyranosides (compounds type **VII**). Glycosides bearing a propargyl moiety were engaged in "click" chemistry reactions leading to the corresponding 1,2,3-triazoles (compounds type **VIII**–**IX**).



VI X = O
VII X = $CHCO_2Et$

VIII X = O
IX X = $CHCO_2Et$

Among the molecular targets obtained, the furanose-linked butenolides, the pyranose-fused butenolides, the conjugated carbonyl sugar derivatives synthesized from CMGLs and the triazole-containing glycosides were submitted to antimicrobial activity assays.

The butenolide-containing sugars did not show satisfactory antibacterial or antifungal activities. Such weak effect is probably due to the presence of a quaternary β-carbon in the conjugated system of these molecules, which is specially hindered in the fused systems, reducing their Michael acceptor ability.

In contrast, significant efficacy was observed for 3-enopyranosid-2-uloses and conjugated diene pyranosides. In particular, (*N*-dodecylcarbamoyl)methyl enulosides

displayed strong and very strong activities against some of the pathogen microbes tested, being in some cases similar to those of the standard antibiotics. The α-enuloside exhibited very strong effect towards *Bacillus cereus* and *Bacillus subtillis* and strong activity against *Enterococcus faecalis* and the fungal pathogen *Penicillium aurantiogriseum*. The β-anomer presented a very strong inhibitory effect against the fungi *Aspergillus niger* and *Penicillium aurantiogriseum*. Dienepyranosides exhibited a strong activity selectively towards *Enterococcus faecalis*. Triazole derivatives were virtually ineffective. Three of the bioactive compounds, including the most active one, i.e. the α-(*N*-dodecylcarbamoyl)methyl enuloside, showed low acute toxicity in eukaryotic hepatoma cells.

Resumo

O trabalho desenvolvido no âmbito deste Doutoramento centrou-se na síntese e no uso de biciclolactonas glicídicas com o objectivo de se obterem novos derivados de açúcares contendo um sistema carbonílico α,β-insaturado na sua estrutura. Estes alvos moleculares foram sintetizados no sentido de se avaliarem posteriormente as suas propriedades biológicas, nomeadamente a nível de actividade antifúngica e antibacteriana.

O sistema carbonílico α,β-insaturado é frequentemente encontrado em produtos naturais e de síntese que possuem uma variedade de actividades biológicas. A bioactividade exibida por estes compostos está geralmente associada à capacidade da função conjugada para reagir segundo adição de Michael com nucleófilos existentes em proteínas. Em particular, derivados de açúcares contendo lactonas α,β-insaturadas foram descritos como fungicidas ou como insecticidas potentes. Por outro lado, a inclusão destas unidades em carbo-hidratos conduz a moléculas funcionalizadas que poderão ser úteis para posterior derivatização, devido à reactividade do sistema conjugado.

As moléculas-alvo tiveram como base três tipos de lactonas bicíclicas (Fig. 1): butenolidas ligadas a anéis de furanose (compostos tipo **I**), butenolidas fundidas a anéis de pyranose, incluindo tio- e iminoaçúcares análogos (compostos tipo **II**–**IV**), e lactonas derivadas de glicósidos de carboximetilo (compostos tipo **V**).

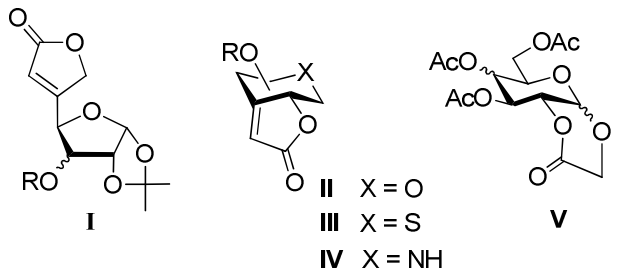
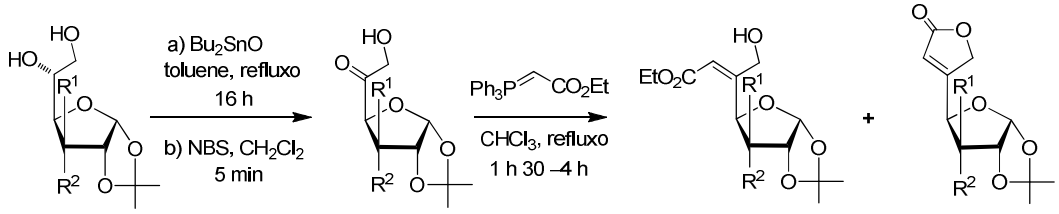


Fig. 1. Estrutura geral das biciclolactonas glicídicas exploradas no presente trabalho.

A síntese de açúcares contendo butenolidas foi desenvolvida e implementada uma metodologia que envolveu a olefinação de Wittig de 3- ou 5-cetoaçúcares e a

lactonização intramolecular expontânea de intermediários γ-hidroxiésters α,β-insaturados formados. Os 5-cetoaçúcares precursores de butenolidas ligadas a furanoses foram obtidos por meio de oxidação selectiva do grupo hidroxilo secundário de 5,6-dióis derivados de 1,2-*O*-isopropilideno-α-D-glucofuranose e/ou -alofuranose (**1**–**4**, Esquema 1). O oxidante utilizado foi o sistema Bu_2OSn/NBS (*N*-bromosuccinimida), dando origem às α-hidroxicetonas desejadas **5**–**8** com bons rendimentos. A estereoselectividade da reacção de Wittig subsequente com [(etoxicarbonil)metileno]trifenilfosforano foi influenciada pela configuração do substituinte em C-3. Os derivados com configuração *xilo* **5** e **6** originaram apenas γ-hidroxiésteres insaturados (**9**, **10**) com estereoquímica (Z). Contudo, utilizando as α-hidroxicetonas com configuração *ribo* **7** e **8**, a reacção de Wittig foi estereosseletiva para a formação dos (*E*)-isómeros, cuja transesterificação intramolecular espontânea deu origem às correspondentes lactonas α,β-insaturadas **13** e **14**. Os (*Z*)-isómeros (**11** e **12)** foram neste caso produtos minoritários da reacção.



1 R^1 = OBn, R^2 = H
2 R^1 = OAll, R^2 = H
3 R^1 = H, R^2 = OBn
4 R^1 = H, R^2 = OAll

5 R^1 = OBn, R^2 = H 90%
6 R^1 = OAll, R^2 = H 78%
7 R^1 = H, R^2 = OBn 60%
8 R^1 = H, R^2 = OAll 61%

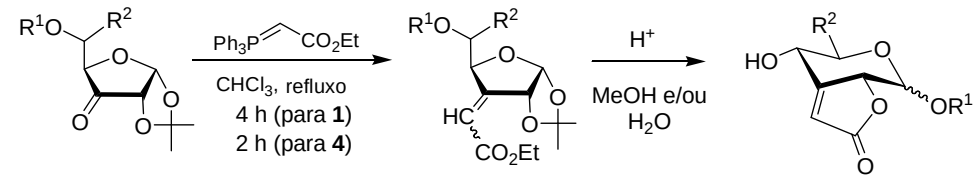
9 R^1 = OBn, R^2 = H 74%
10 R^1 = OAll, R^2 = H 60%
11 R^1 = H, R^2 = OBn 12%
12 R^1 = H, R^2 = OAll 11%

13 R^1 = H, R^2 = OBn 47%
14 R^1 = H, R^2 = OAll 49%

Esquema 1. Síntese de butenolidas ligadas a furanoses por uma ligação C-C ou dos respectivos ésteres a partir dos 5-cetoaçúcares **5**–**8**.

A estratégia implementada para a síntese de butenolidas fundidas a piranoses (compostos tipo **II,** Fig. 1) baseou-se na olefinação de Wittig de derivados 1,2-*O*-isopropilideno-α-D-pento- ou-hexofuranos-3-ulose, 5-*O*- ou 5,6-di-*O*-protegidos com grupos lábeis em meio ácido, seguida de hidrólise ácida. Nestas condições, com a remoção dos grupos protectores, além da reacção de transesterificação intramolecular que leva à formação da lactona, também ocorre isomerização furanose → piranose, conduzindo à síntese das moléculas alvo num só passo.

A olefinação de Wittig dos 3-cetoaçúcares **15** e **16** foi estereosselectiva para a formação dos respectivos ésteres (*Z*)-α,β-insaturados **17a** e **18a** (Esquema 2). O tratamento de **17a** e **18a** com a resina ácida Amberlite em refluxo de metanol durante 16 h levou à formação dos compostos-alvo **19** e **21**.



15 $R^2 = CH_2OR^3$; $R^1,R^3 = C(CH_3)_2$

16 R^1 = TBDMS, R^2 = H

17a (isómero-*Z*) 68%

17b (isómero-*E*) 12%

18a (isómero-*Z*) 81%

18b (isómero-*E*) 8%

19 R^1 = H, R = CH_2OH 90%

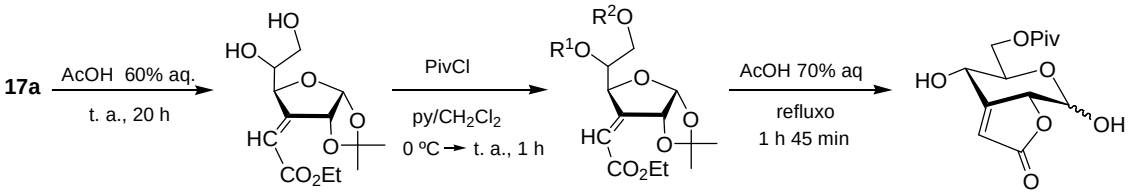
20 R^1 = Me, R = CH_2OH 57%

21 R^1, R^2 = H 79%

Esquema 2. Via de síntese de butenolidas fundidas a piranoses.

As condições experimentais de hidrólise de **17a** foram optimizadas de modo a reduzir o tempo de reacção para a obtenção do composto bicíclico **19** e também para permitir a formação do correspondente glicósido de metilo **20**. A hidrólise de **17a** com uma solução aquosa de ácido trifluoroacético (TFA) a 60%, à temperatura ambiente, conduziu ao composto bicíclico desejado **19** em apenas 5 min, com um rendimento de 90%. Utilizando a resina Dowex 50-W, a conversão de **17a** em **19** foi completa ao fim de 2 h e, após 16 h de reacção, obteve-se o glicósido de metilo **20**.

A síntese de um derivado bicíclico regiosselectivamente protegido no grupo hidroxilo primário (composto **25**, Esquema 3) foi realizada a partir da monoprotecção selectiva do diol **22** com cloreto de pivaloílo seguida da hidrólise em meio ácido.



22 95%

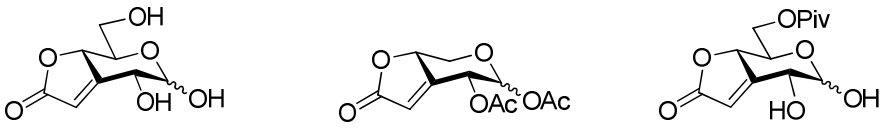
23 R^1 = H, R^2 = Piv 57%

24 R^1 = R^2 = Piv 27%

25 86%

Esquema 3. Síntese do derivado **25** regiosselectivamente protegido em OH-6.

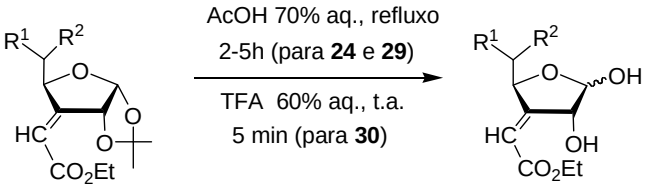
Analogamente e seguindo a mesma estratégia de síntese, a partir dos ésteres (*E*)-insaturados **17b** e **18b**, foram obtidos, com sucesso, os compostos **26**–**28**, nos quais a unidade butenolida está fundida ao anel de piranose nas posições 3 e 4 (Fig. 2).



26 **27** **28**

Fig. 2. Estrutura dos derivados de açúcares sintetizados nos quais a unidade butenolida se encontra fundida ao anel de piranose nas posições 3 e 4.

No entanto não se verificou lactonização após remoção do grupo 1,2-isopropilideno do derivado 5,6-di-*O*-pivaloílado **24**, e dos derivados pentofuranóides com configuração *erythro*, possuindo um grupo pivaloilo em C-5 (**29**) ou desoxigenado em C-5 (**30**), nas condições hidrolíticas descritas e obtiveram-se os respectivos dióis **31**–**33** (Esquema 4). Estes resultados indicam que a fusão de lactonas insaturadas de cinco membros a anéis de furanose é desfavorável, ocorrendo preferencialmente em sistemas de piranose.



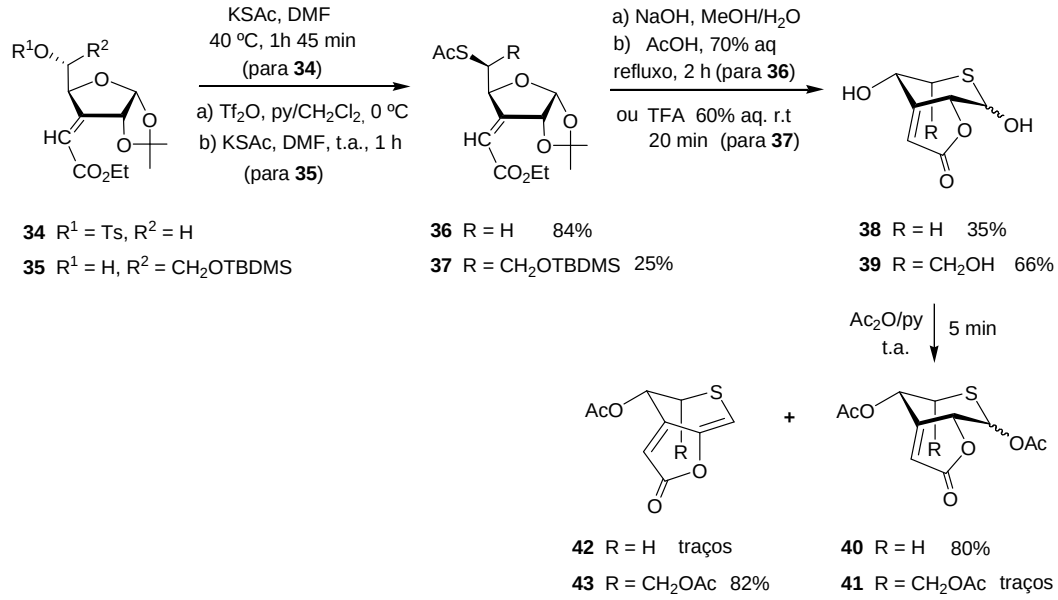
24 R^1 = OPiv, R^2 = CH_2OPiv — **31** 62%
29 R^1 = OPiv, R^2 = H — **32** 70%
30 R^1, R^2 = H — **33** 56%

Esquema 4. Hidrólise de **24**, **29** e **30** dando origem aos dióis **31**–**33**.

A eficácia e a conveniência desta metodologia para a obtenção de análogos tioaçúcares e iminoaçúcares (compostos tipo **III e IV**, Fig. 1), a partir de furanos-3-uloses, foram também investigadas. A estas duas classes de miméticos de carbo-hidratos está frequentemente associada uma variedade de propriedades biológicas, nomeadamente a capacidade de inibição de glicosidases. O interesse neste tipo de estruturas reside

também no seu potencial sintético como precursores para novos derivados de tio- e iminoaçúcares.

A síntese de butenolidas fundidas a tioaçúcares involveu a introdução de uma função sulfidrílica em C-5 nos derivados (*Z*)-3-*C*-(etoxicarbonil)metileno pento- ou hexofuranóides **34** e **35** por meio de substituição nucleófila de um grupo tosilato ou de um triflato, respectivamente, por um grupo tioacetilo (Esquema 5). A remoção dos grupos éster de **36**, **37** seguida de hidrólise ácida deu origem aos compostos bicíclicos desejados **38** e **39**. A posterior acetilação de **38 e 39** conduziu aos derivados acetilados **40** e **41** e aos tioglicais correspondentes **42** e **43**, por eliminação de ácido acético. A acetilação de **39** conduziu maioritariamente ao tioglical **43**, o que pode ser explicado pela baixa estabilidade conformacional de **41,** devido à presença de um grupo acetoximetilo pseudoaxial. A eliminação em C-1,C-2 não só resulta num sistema conjugado altamente estável, mas no caso de **41** permite a adopção de uma conformação *sofá* relativamente estável.

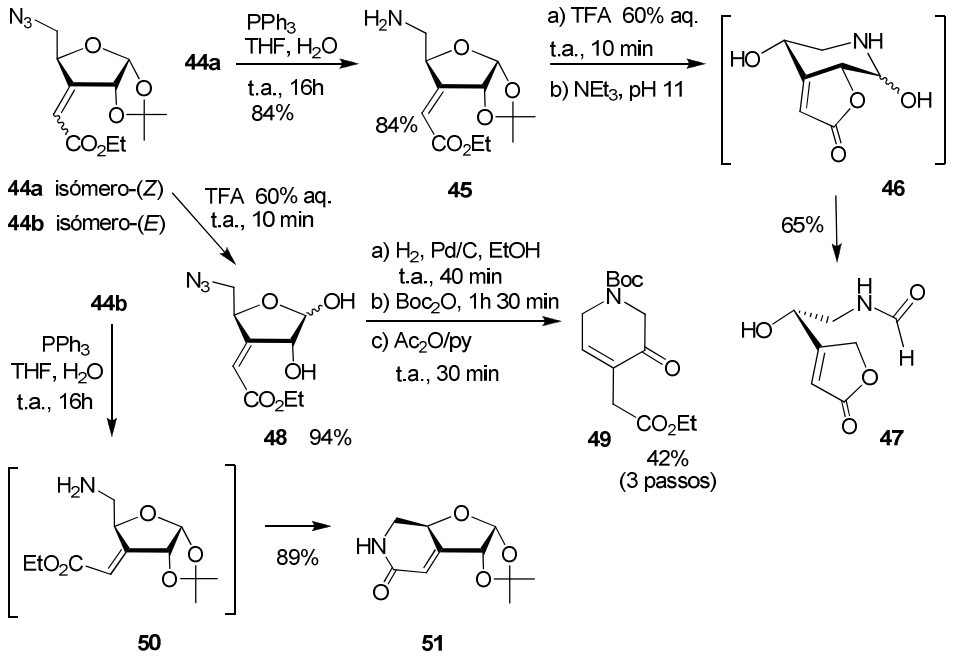


Esquema 5. Síntese de butenolidas fundidas a 5-tiopento- e 5-tiohexopiranoses.

Para a investigação da síntese de iminoaçúcares do tipo **IV** foram sintetizados os precursores 5-azido-3-*C*-(etoxicarbonil)metileno furanoses (**44**, Esquema 6). A redução do grupo azida do éster (*Z*)-α,β-insaturado **44a** pelo método de Staudinger resultou na

respectiva amina **45.** A hidrólise de **45** em meio ácido seguida de adição de base para neutralizar o ácido em excesso, resultou no derivado da etilformamida contendo uma butenolida **47**. A formação do composto **47** involve o intermediário bicíclico **46**, o qual em meio básico é desprotonado no grupo hidroxilo anomérico. O ião resultante rearranja para um ião enolato estabilizado por ressonância, que é protonado em C-2.

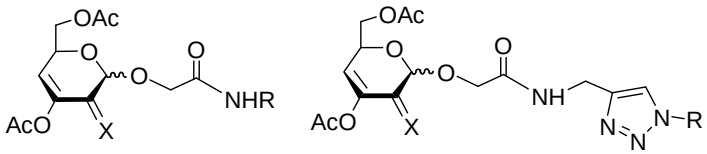
A hidrólise ácida do grupo 1,2-*O*-isopropilideno de **44a** e posterior redução da função azida do diol **48**, de modo a permitir a isomerização 5-aminofuranose/iminopiranose em meio neutro, resultou num 2-cetoiminoaçúcar que por acetilação originou a 1,2-di-hidropiridin-3-ona **49**. A redução do grupo azida do (*E*)-isómero (**44b**) deu origem à δ-lactama bicíclica **51** por ciclização intramolecular expontânea do δ-aminoéster α,β-insaturado **50**.



Esquema 6. Exploração de 5-azido-3-*C*-(etoxicarbonil)metileno furanose como sintão para uma variedade de derivados de açúcares contendo um sistema carbonílico α,β-insaturado.

Os derivados 5-aminofuranóides revelaram portanto uma reactividade distinta relativamente aos análogos 5-*O* e 5-*S*, que em condições reaccionais semelhantes originaram as butenolidas bicíclicas alvo.

As biciclolactonas derivadas de glicósidos de carboximetilo (CMGLs, compostos tipo **V**, Fig. 1), cuja preparação envolve 2-3 etapas a partir de açúcares livres, foram utilizadas como precursores de cetonas piranóides α,β-insaturadas do tipo hex-3-enopiranosid-2-ulose e de dienopiranósidos conjugados (compostos tipo **VI**–**VII**, Fig. 3). A inclusão de uma unidade 1,2,3-triazole, um heterociclo com potencial para conferir bioactividade, para a obtenção de derivados do tipo **VIII**–**IX,** foi também investigada.



VI X = O
VII X = $CHCO_2Et$

VIII X = O
IX X = $CHCO_2Et$

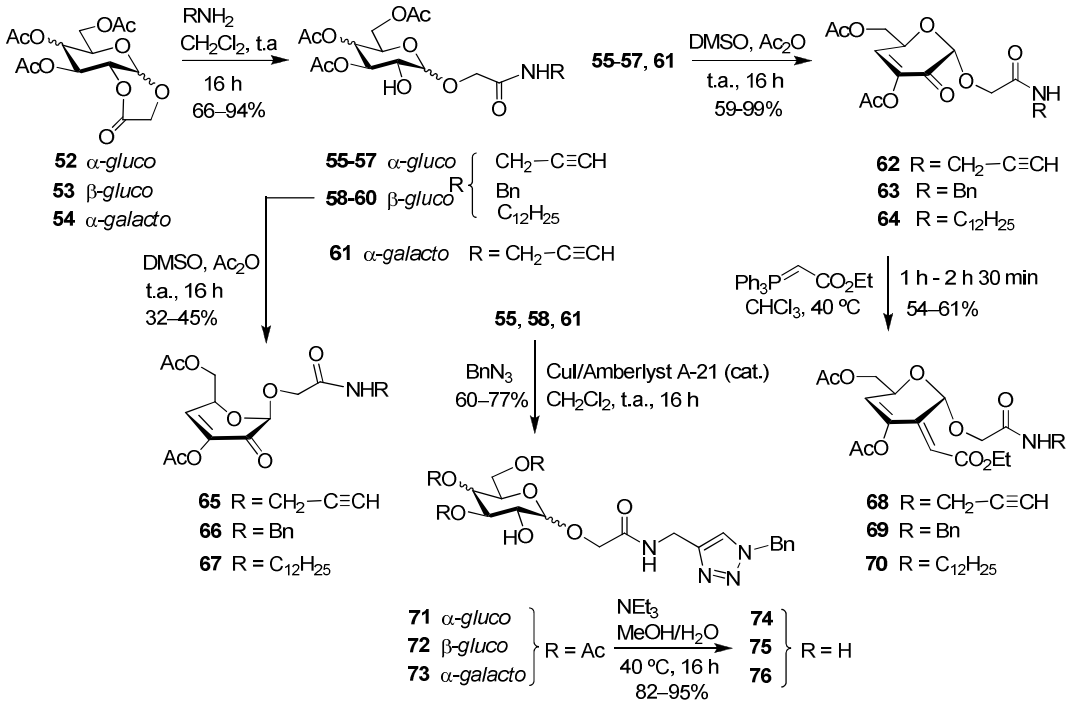
Fig. 3. Estrutura geral dos compostos-alvo contendo uma função carbonílica conjugada e uma unidade 1,2,3-triazole cuja síntese envolveu precursores CMGLs.

A preparação de cetonas α,β-insaturadas do tipo **VI** consistiu na abertura nucleófila de CMGLs **52**-**54** com aminas primárias, seguida de oxidação dos aductos resultantes e eliminação concomitante de ácido acético nas posições 3,4 (Esquema 7). O método de oxidação utilizando o sistema dimetilsulfóxido (DMSO)/anidrido acético (Ac_2O) revelou ser o mais eficaz em experiências preliminares e permitiu a obtenção do sistema enona com melhores rendimentos, em relação a outros métodos de oxidação mais suaves.

Os 2-hidroxipyranósidos tri-*O*-acetilados **55**–**57**, **61** com configuração α, conduziram às respectivas enonas **62**–**64** com bons rendimentos. No entanto, os rendimentos para a oxidação/eliminação dos aductos β (**58**-**60**) foram baixos e as respectivas enonas **65**–**67** demonstraram a sua tendência para a decomposição. Estes resultados devem-se à conformação adoptada por estes compostos, tal como verificado por ^{1}H RMN. Enquanto as enonas **62**–**64** adoptam uma conformação do tipo envelope ^{O}E (*sofá*), os respectivos anómeros β adoptam uma conformação E_O, que é menos estável devido às interacções 1,3-diaxiais. As cetonas α,β-insaturadas foram posteriormente convertidas nos correspondentes dienopiranósidos de cadeia ramificada em C-2 (**68**–**70**) por olefinação

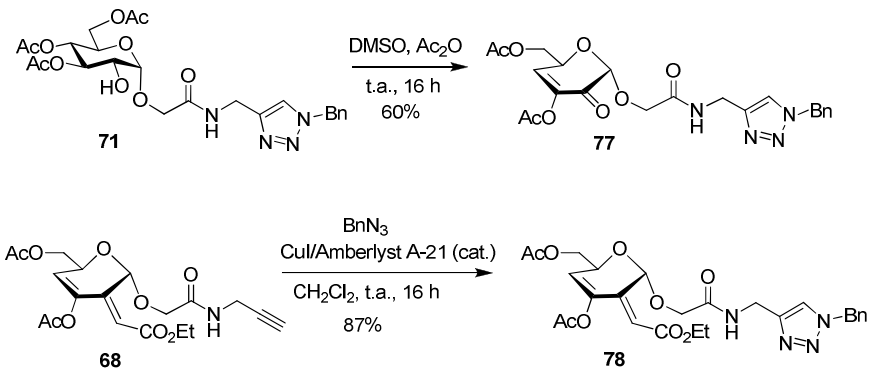
de Wittig com [(etoxicarbonil)metileno]trifenilfosforano. A configuração (*E*) da ligação dupla exocíclica foi demonstrada através de NOESY.

As reacções de cicloadição dos glicósidos de (*N*-propargilcarbamoil)metilo **55**, **58** e **61** com azoteto de benzilo por meio de um protocolo alternativo de *'click' chemistry*, tendo como base um catalisador heterogéneo de CuI suportado em Amberlist A-21, deu origem aos triazoles correspondentes **71-73.** Os derivados desprotegidos **74-76** foram seguidamente obtidos por desacetilação com NEt_3 em metanol e água.



Esquema 7. Investigação de CMGLs como precursores de 3-enopiranosid-2-uloses, dieno piranósidos conjugados e glicósidos contendo um anel 1,2,3-triazole.

A síntese dos compostos do tipo **VIII** e **IX**, os quais associam numa molécula um sistema carbonílico conjugado a uma unidade triazole, foi realizada posteriormente (Esquema 8). A oxidação/eliminação de **71** conduziu à 3-enopiranosid-2-ulose **77**. O acoplamento do dieno piranósido conjugado **68** com azoteto de benzilo originou o triazole correspondente **78**.



Esquema 8. Síntese de derivados piranosídicos contendo um sistema carbonílico conjugado e uma unidade 1,2,3-triazole.

Entre os alvos moleculares obtidos, os derivados bicíclicos nos quais uma butenolida se encontra ligada a um anel de furanose (compostos tipo **I**), as butenolidas fundidas a anéis de piranose (compostos tipo **II**), os derivados piranóides contendo um sistema carbonílico conjugado sintetizados a partir dos precursores CMGLs (compostos tipo **VI**–**VII**) e os glicósidos contendo uma unidade triazole (compostos tipo **VIII**–**IX**), foram submetidos a testes de actividade antimicrobiana. Foi investigada a inibição de fungos fitopatogénicos e de fungos patogénicos para seres humanos e animais. Foi também feito um estudo sobre a actividade inibidora dos compostos relativamente a bactérias Gram-negativas e Gram-positivas.

Os derivados de açúcares contendo butenolidas apresentaram fraca actividade antimicrobiana ou não a exibiram de modo significativo. Estes resultados sugerem uma reduzida aptidão destas moléculas para reagir segundo a adição de Michael, o que se explica pela presença de um C-β quaternário no sistema conjugado, que é estereoquimicamente impedido nas estruturas fundidas.

No entanto, os resultados da avaliação biológica das 3-enopiranosid-2-uloses e dos dienopiranósidos de cadeia ramificada revelaram actividades antimicrobianas significativas. Os enulósidos de (*N*-dodecilcarbamoil)metilo **64** e **67** exibiram actividades fortes ou muito fortes contra alguns dos micróbios testados, demonstrando nalguns casos efeitos inibitórios comparáveis aos dos antibióticos de referência. O enulósido-α (**64**) revelou actividade muito forte relativamente às bactérias *Bacillus cereus* e *Bacillus subtillis* e actividade forte contra *Enterococcus faecalis* e o fungo

Penicillium aurantiogriseum. O anómero-β (**67**) exibiu um efeito inibitório muito forte contra os fungos *Aspergillus niger* e *Penicillium aurantiogriseum*. Os dienopiranósidos conjugados **68**–**70** revelaram actividade selectiva e forte relativamente a *Enterococcus faecalis*. Os derivados contendo triazole não demonstraram actividade antimicrobiana significativa. Três dos compostos considerados bioactivos, o α-enulósido de (*N*-dodecilcarbamoil)metilo **64**, e os dienopiranósidos **68** e **69**, mostraram ser pouco tóxicos quando submetidos a testes de toxicidade em células eucarióticas hepáticas.

Résumé

Le travail développé dans le cadre de ce sujet de thèse porte sur la synthèse et utilisation de bicyclolactones glycidiques, de façon à accéder des nouveaux dérivés de sucres contenant un système carbonylé α,β-insaturé dans leur structure. Ces cibles moléculaires ont été synthétisées afin d'évaluer certaines propriétés biologiques, notamment leur activité antibactérienne et fongicide.

Le système carbonylé α,β-insaturé est présent dans un grand nombre de produits naturels et synthétiques possédant une variété d'activités biologiques. La bioactivité de ces composés est souvent associée à la capacité du système conjugué à réagir comme accepteur de Michael pour l'addition de fonctions nucléophiles des protéines. En particulier, les dérivés glucidiques contenant des lactones α,β-insaturées ont été décrites comme puissantes fongicides et insecticides. De plus, l'inclusion de ces unités dans les carbohydrates conduit à des molécules fonctionnalisées qui peuvent être utiles pour dérivatisation, en raison de la réactivité du système conjugué.

Les molécules cibles sont basées sur trois types de lactones bicycliques (Fig. 1): butenolides liés à des cycles furanose (composés du type **I**), butenolides fusionnés à des cycles pyranose, comprenant aussi leurs analogues tio- et iminosucres (composés du type **II**–**IV**) et lactones dérivées de glycosides de carboxyméthyle (composés du type **V**).

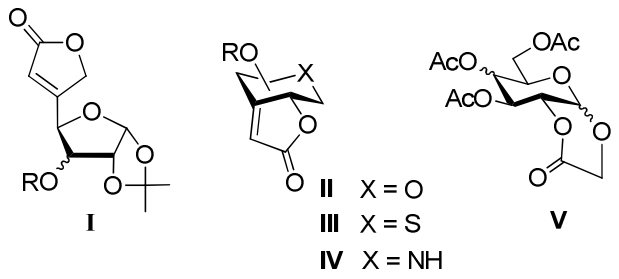
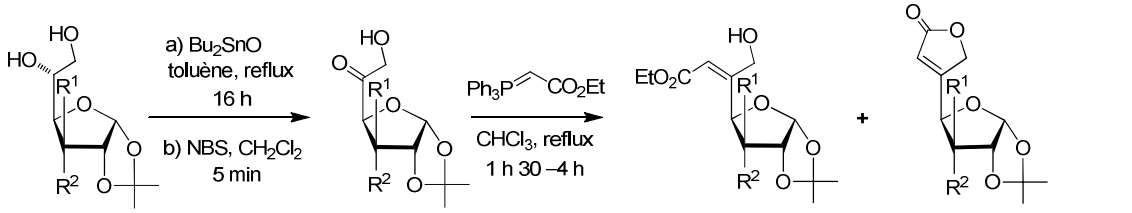


Fig. 1. Structure générale des bicyclolactones glycidiques explorées dans ce travail.

Une méthodologie de synthèse de butenolides construits sur châssis glucidique a été développée. Elle est basée sur l'oléfination de Wittig de 3 ou 5-cétosucres et

lactonisation intramoléculaire spontanée de γ-hydroxyesters α,β-insaturés intermédiaires. Les 5-cétosucres précurseurs de butenolides liés à des cycles furanose ont été obtenus par oxydation sélective de la fonction secondaire des diols-5,6 dérivés du 1,2-*O*-isopropylidène-α-D-glucofuranose et/ou -allofuranose (**1**–**4**, Schéma 2). L'oxydant utilisé est le système Bu_2SnO/NBS (*N*-bromosuccinimide), ce qui a conduit aux hydroxycétones desirées **5**–**8** avec des bons rendements. La stéréosélectivité de la réaction suivante, une réaction de Wittig avec l'ylure stabilisé, [(éthoxycarbonyl)metilène]triphénylphosphorane, dépend de la configuration du substituant en C-3. Les dérivés de configuration *xylo* **5** et **6** ont conduit uniquement aux hydroxyesters insaturés **9**, **10** de stéréochimie (*Z*). Par contre, les α-hydroxycétones de configuration *ribo* (**7** et **8**), conduisent majoritairement aux isomères (*E*), dont la transestérification intramoléculaire spontanée a permis d'obtenir les lactones α,β-insaturées **13** et **14**. Dans ce cas, les isomères (*Z*) (**11**, **12**) sont minoritaires.



1 R^1 = OBn, R^2 = H
2 R^1 = OAll, R^2 = H
3 R^1 = H, R^2 = OBn
4 R^1 = H, R^2 = OAll

5 R^1 = OBn, R^2 = H 90%
6 R^1 = OAll, R^2 = H 78%
7 R^1 = H, R^2 = OBn 60%
8 R^1 = H, R^2 = OAll 61%

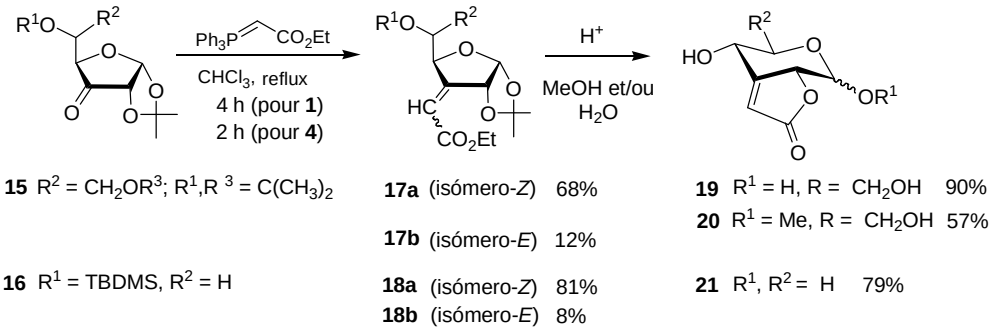
9 R^1 = OBn, R^2 = H 74%
10 R^1 = OAll, R^2 = H 60%
11 R^1 = H, R^2 = OBn 12%
12 R^1 = H, R^2 = OAll 11%

13 R^1 = H, R^2 = OBn 47%
14 R^1 = H, R^2 = OAll 49%

Schéma 1. Synthèse de butenolides liées aux furanoses par une liaison C-C ou des γ-hydroxyesters α,β-insaturés à partir des 5-cétosucres **5**–**8**.

La stratégie mise en pratique pour la synthèse de butenolides fusionnés aux pyranoses est basée sur l'oléfination de Wittig de dérives 1,2-O-isopropylidène-α-D-pento- ou -hexofuranos-3-uloses 5-*O*- ou 5,6-di-*O*-protégés avec des groupements labiles en millieu acide, suivie d'une hydrolyse acide. En conséquence, la suppression des groupements protecteurs permet la transestérification intramoléculaire qui conduit à la formation de la lactone, et l'isomérization furanose → pyranose, conduisant en une seule étape aux molécules cibles.

L'oléfination de Wittig des 3-cétosucres **15** et **16** s'est révélée stéréosélective pour la formation des correspondants esters (*Z*)-α,β-insaturés **17** et 1**8** (Schéma 2). Le traitement de **17a** et **18a** avec de la résine acide Amberlite dans du méthanol au reflux pendant 16 h a conduit à la formation de composés cibles **19** et **21**.



15 $R^2 = CH_2OR^3$; $R^1,R^3 = C(CH_3)_2$

16 R^1 = TBDMS, R^2 = H

17a (isómero-*Z*) 68%

17b (isómero-*E*) 12%

18a (isómero-*Z*) 81%

18b (isómero-*E*) 8%

19 R^1 = H, R = CH_2OH 90%

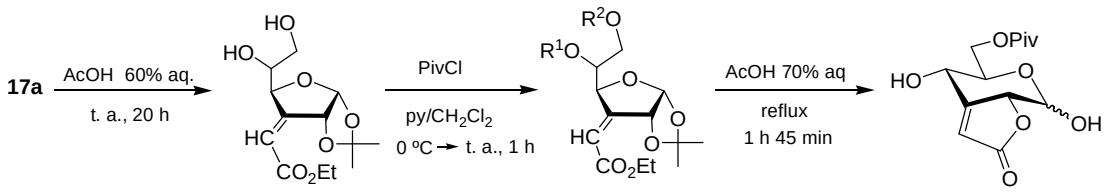
20 R^1 = Me, R = CH_2OH 57%

21 R^1, R^2 = H 79%

Schéma 2. Voie de synthèse de butenolides fusionnés à des cycles pyranose.

Les conditions expérimentales de l'hydrolyse de **17a** ont été optimisées pour réduire le temps de réaction et pour orienter vers la formation du composé bicyclique **19** ou du glycoside de méthyle **20**. L'hydrolyse de **17a** avec du TFA (acide trifluoroacétique) aqueux à 60% à température ambiante conduit au composé **19** en 5 min, avec un rendement de 90%. En utilisant la résine Dowex 50-W, la conversion de **17a** en **19** a été complète en 2 h, et après 16 heures de réaction, le glycoside de méthyle **20** a été obtenu.

La synthèse d'un dérivé bicyclique régiosélectivement protégé sur l'hydroxyle primaire (composé **25**, Schéma 3) a été réalisée par monoprotection sélective du diol **22** avec du chlorure de pivaloyle suivie d'une hydrolyse en milieu acide.



22 95%

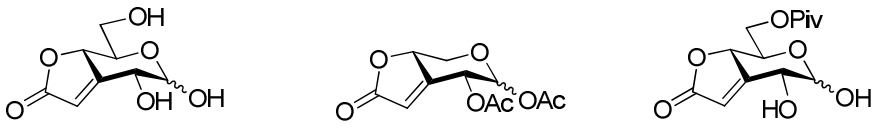
23 R^1 = H, R^2 = Piv 57%

24 $R^1 = R^2$ = Piv 27%

25 86%

Schéma 3. Synthèse du dérivé **25** protégé régiosélectivement dans OH-6.

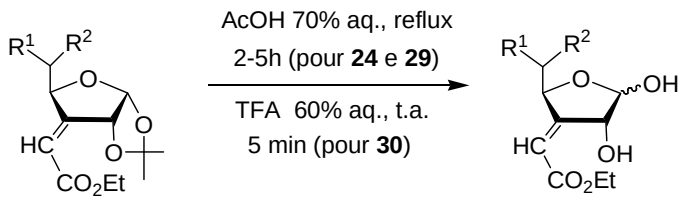
De la même façon, en suivant la même stratégie de synthèse, à partir des esters insaturés **17b** et **18b** de géometrie (*E*), les composés **26**–**28**, dans lesquels l'unité butenolide est fusionnée à un cycle pyranose en positions 3 et 4, ont été obtenus avec succès (Fig. 2).



26 **27** **28**

Fig. 2. Structures des dérivés glycidiques dans lesquel l'unité butenolide est fusionnée à un cycle pyranose en positions 3 et 4.

Cependant, après la supression du groupe 1,2-*O*-isopropylidène du derivé 5,6-di-*O*-pivaloylé **24** et des dérivés pentofuranosidiques de configuration *erythro*, possédant un groupement pivaloyle en C-5 (**29**) ou désoxygénée en C-5 (**30**), la lactonisation n'a pas été observée dans les conditions d'hydrolyse précédemment utilisées et les diols correspondants **31**–**33** ont été obtenus (Schéma 4). Ces résultats indiquent que la fusion des lactones insaturées à cinq chaînons à des cycles furanose est défavorable, mais survient préférentiellement dans les systèmes de pyranose.



24 R^1 = OPiv, R^2 = CH_2OPiv — **31** 62%
29 R^1 = OPiv, R^2 = H — **32** 70%
30 R^1, R^2 = H — **33** 56%

Schéma 4. Hydrolyse de **24**, **29** et **30** conduisant aux diols **31**–**33**.

L'efficacité de cette méthode pour obtenir des analogues thiosucres et imino sucres (composés du type **III** et **IV**, Fig. 1) à partir de furanos-3-uloses a ensuite été étudiée. Ces deux classes de mimes de sucres (« carbohydrate mimetics ») sont souvent associées à une variété de propriétés biologiques, notamment à la capacité d'inhiber glycosidases.

L'intérêt pour ces structures réside aussi sur leur potentiel synthétique comme précurseurs de nouveaux dérivés de thio- et iminosucres.

La synthèse de butenolides fusionnés à des thiosucres a impliqué l'introduction d'une fonction sulfhydryle en position 5 des dérivés (*Z*)-3-*C*-(éthoxycarbonyl)metilène pento- ou hexofuranosidiques **34** et **35** par substitution nucléophile d'un groupement tosylate ou d'un triflate, respectivement, par un groupement tioacetyle (Schéma 5). La déprotection des groupements ester de **36**, **37** suivie de l'hydrolyse acide a donné les composés bicycliques desirés **38** et **39.** L'acétylation subséquente de **38** et **39** a conduit aux dérivés **40** et **41** et aux thioglycals correspondants **42** et **43**, par élimination d'acide acétique. L'acétylation de **39** à conduit majoritairement au thioglycal **43**, ce qui peut s'expliquer par la faible stabilité conformationnelle de **41**, en raison de la présence d'un groupement acétoxyméthyle pseudoaxial. L'élimination en C-1,C-2 dans le cas de **40** ou de **41**, donne un système conjugué très stable. De plus, pour **41**, la molécule peut adopter une conformation *sofa* relativement stable.

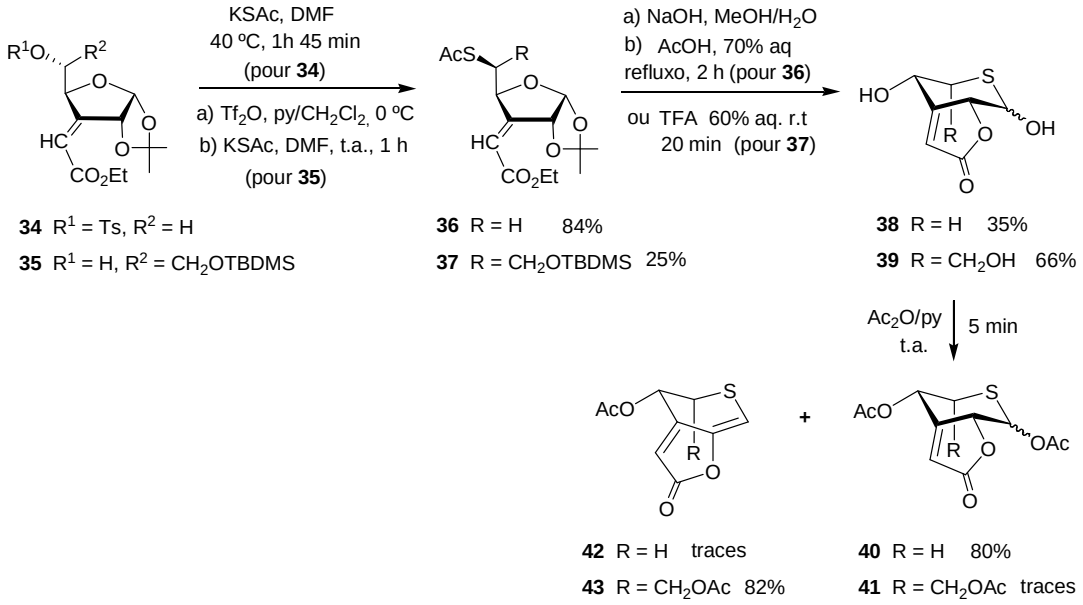


Schéma 5. Synthèse de butenolides fusionnés à des motifs 5-thiopento- et 5-thiohexopyranoses.

Pour étudier la synthèse des iminosucres du type **IV**, des précurseurs 5-azido-3-*C*-(éthoxycarbonyl)méthylène furanosidiques ont été synthétisés (**44**, Schéma 6). La

réduction du groupement azide de l'ester (Z)-α,β-insaturé **44e** par la méthode de Staudinger a donnée l'amine correspondante **45**. L'hydrolyse de **45** en milieu acide suivie d'addition de base pour neutraliser l'acide en excès, a conduit à un dérivé de l'éthylformamide contenant un butenolide (**47**). La formation du composé **47** implique l'intermédiaire bicyclique **46**, dont l'hydroxyle anomérique est déprotoné en milieu basique. L'ion résultant se réarrange pour donner un ion énolate, stabilisé par résonance, qui est ensuite protoné en C-2.

Après hydrolyse acide du groupement 1,2-*O*-isopropylidène du composé **44a**, et la réduction de la fonction azide du diol **48**, qui permet l'isomérisation 5-aminofuranose/iminopiranose en milieu neutre, qui conduit à un 2-céto iminosucre, une acétylation finale forme la 1,2-dihydropyridine-3-one **49**. La réduction du groupe azide de l'isomère (*E*) (**44b**) a conduit à la δ-lactame bicyclique **51** par cyclisation intramoléculaire spontanée du δ-aminoester α,β-insaturé **50**.

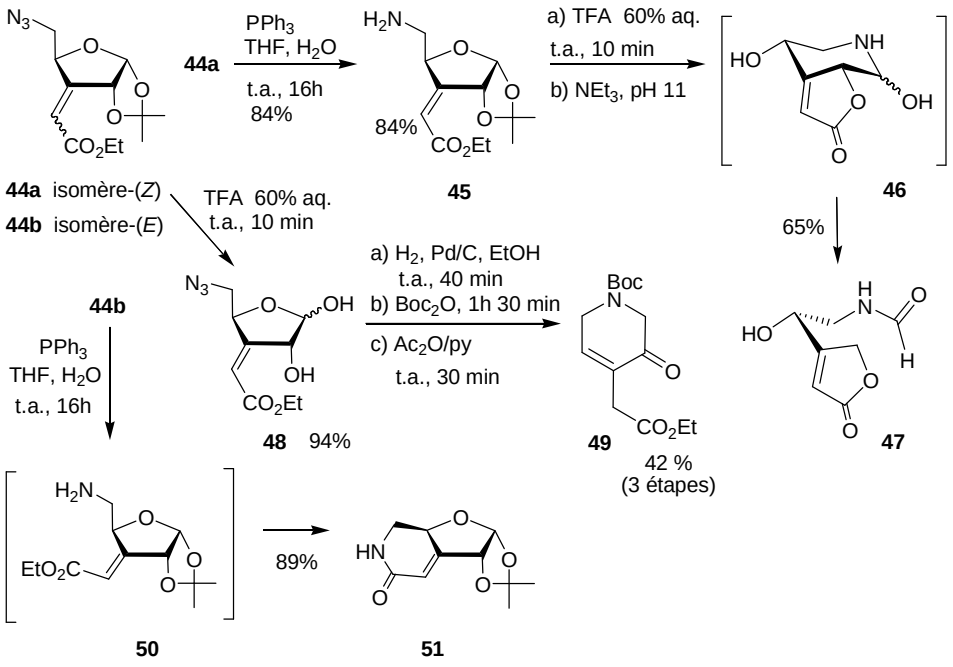
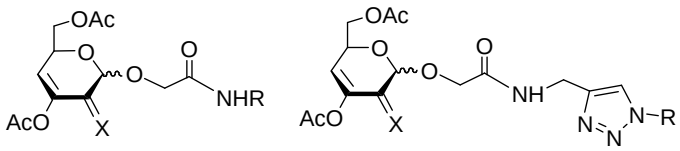


Schéma 6. Exploration de 5-azido-3-C-(éthoxycarbonyl)méthylène furanoses comme synthons pour une variété de derivés glycidiques contenant un système carbonylé α,β-insaturé.

Les dérivés 5-amino furanosidiques ont donc montré une réactivité distincte par rapport aux analogues 5-*O* et 5-*S*, qui, dans des conditions réactionelles similaires, ont conduit aux butenolides bicycliques attendues.

Les bicyclolactones dérivées de glycosides de carboxyméthyle (CMGLs, composés de type **V**, Fig. 1), dont la préparation comporte 2- à 3 étapes à partir de sucres libres, ont été utilisés comme précurseurs de cétones pyranoïdes α,β-insaturées du type hex-3-enopyranosid-2-ulose et de dièpepyranosides conjugués (composés de type **VI**–**VII**, Fig. 3). L'inclusion d'une unité 1,2,3-triazole, un hétérocycle susceptible de conférer bioactivité, afin d'obtenir les dérivés du type **VIII**–**IX**, a également été étudiée.



VI X = O
VII X = $CHCO_2Et$

VIII X = O
IX X = $CHCO_2Et$

Fig. 3. Structure général des molécules cible contenant un système carbonylé conjugué et un cycle 1,2,3-triazole, dont la préparation implique des précurseurs CMGLs.

La préparation des cétones α,β-insaturées de type **VI** a été basée sur l'ouverture nucléophile des CMGLs **52**–**54** avec des amines primaires, suivie d'oxydation des adduits et d'élimination concomitante d'acide acétique en positions 3,4. (Schéma 7). La méthode d'oxydation par le système diméthylsulfoxyde (DMSO)/anhydride acétique (Ac_2O) s'est révélée la plus efficace lors d'expériences préliminaires, et a permis d'obtenir le système énone avec de meilleurs rendements, par rapport à d'autres méthodes d'oxydation plus douces.

Les 2-hydroxy pyranosides tri-*O*-acétylés **55**–**57**, **61** possédant configuration α ont conduit aux énones **62**–**64** correspondantes avec de bons rendements. Cependant, les rendements de l'oxydation/élimination des adduits β (**58**–**60**) ont été faibles et les énones **65**–**67** ont montré leur tendance à se décomposer. Cela peut être expliqué par la conformation adoptée par ces composés, vérifiée par ^{1}H RMN. Tandis que les énones **62**–**64** (de configuration α) adoptent une conformation envelope ^{O}E (*sofa*), les anomères

β adoptent une conformation E_O, qui est habituellement considérée moins stable à cause des interactions 1,3-diaxiales. Les cétones α,β-insaturées ont ensuite été converties en dièpyranosides conjugués de chaîne ramifiée en C-2 (**68**-**70**) par oléfination de Wittig avec le réactif [(éthoxycarbonyl)metilène]triphénylphosphorane. La configuration (*E*) de la double liaison exocyclique a été vérifiée par NOESY.

Les réactions de cycloaddition des glycosides de (*N*-propargylcarbamoyl)méthyle **55**, **58** et **61** avec l'azoture de benzyle en utilisant un protocole alternatif de '*click' chemistry*, basé sur un catalyseur hétérogène CuI appuyé sur Amberlist A-21, ont donné les triazoles correspondant **71**–**73**. Les dérivés déprotégés **74**–**76** ont ensuite été obtenus par désacétylation avec NEt_3 dans du méthanol et de l'eau.

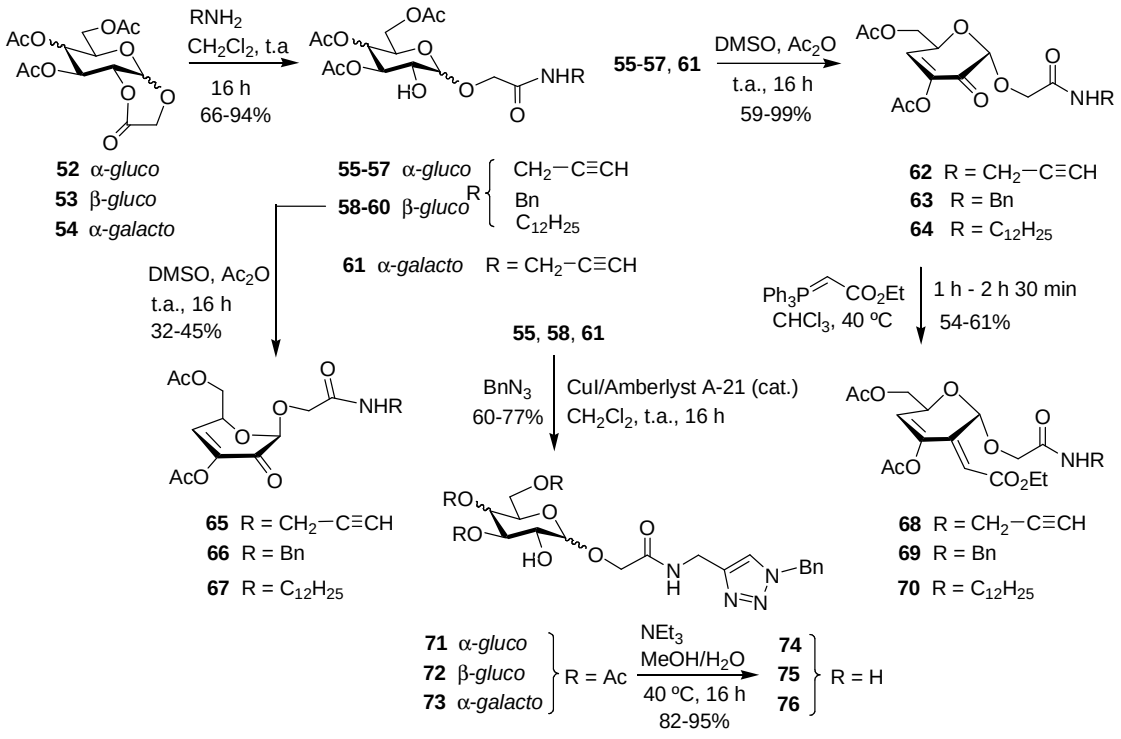


Schéma 7. Exploration de CMGLs comme précurseurs de 3-énopyranosid-2-uloses, dièpyranosides conjugués et de glycosides contenant un cycle 1,2,3-triazole.

La préparation des composés de type **VIII** et **IX**, qui associent dans une molécule un système carbonylé conjugué à une unité de triazole a ensuite été réalisée (Schéma 8). L'oxydation/élimination de **71** a conduit à la 3 enopiranosid-2-ulose **77**. Le couplage du

dièneпyranoside conjugué **68** avec azoture de benzyle a donné le triazole correspondant **78**.

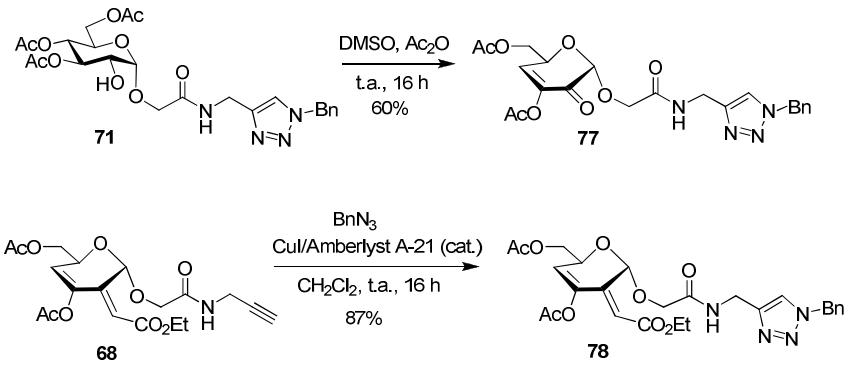


Schéma 8. Synthèse de dérivés pyranosidiques contenant un système carbonylé conjugué et un cycle 1,2,3-triazole.

Parmi les produits obtenues, les dérivés bicycliques dans lesquels un motif butenolide est lié à un cycle furanose (composés de type **I**), les butenolides fusionnés à un cycle pyranose (composés de type **II**), les dérivés pyranoïdes contenant un système carbonylé conjugué synthétisés à partir des précurseurs CMGLs (composés de type **VI**–**VII**) et les glycosides contenant une unité triazole (composés de type **VIII**–**IX**), ont été testés pour leur activité antimicrobienne. L'activité vis à vis de champignons phytopathogènes et de champignons pathogènes pour les humains et pour les animaux a été étudiée. Enfin, une étude sur l'activité sur des bactéries Gram négatif et Gram-positif a été réalisée.

Les dérivés de sucres contenant un motif butenolide ont montré des faibles activités antimicrobiennes ou n'ont pas montré d'activités significatives. Ces résultats suggèrent que ces molécules ont une capacité réduite à réagir comme accepteurs de Michael, ce qui peut être lié à la présence d'un C-β quaternaire dans le système conjugué, lequel est particulièrement encombré dans les structures fusionnées.

Cependant, l'évaluation biologique des 3-enopiranosid-2-uloses et des dièнepyranosides de chaîne ramifiée a révélé des activités antimicrobiennes intéressantes. Les énulosides de (*N*-dodécylcarbamoyl)méthyle **64** et **67**, en particulier, ont montré des activités fortes ou très fortes contre quelques microbes testés, dans certains cas possédant des effets inhibiteurs comparables à ceux des antibiotiques de référence. L'enuloside-α (**64**) a

montré une très forte activité contre la bactérie *Bacillus cereus* et contre *Bacillus subtilis* et une forte activité contre *Enterococcus faecalis* et *Penicillium aurantiogriseum*. L'anomére-β (**67**) a présenté un fort effet inhibiteur contre les champignons *Aspergillus niger* et *Penicillium aurantiogriseum*. Les dièpyranosides conjugués **68**–**70** ont révélé une activité forte et sélective contre *Enterococcus faecalis*. Les dérivés contenant un cycle triazole n'ont montré aucune activité antimicrobienne significative. Trois des composés considérés comme bioactifs, l'α-énuloside de (*N*-dodécylcarbamoyl)méthyle **64** et les dièpyranosides **68** et **69**, se sont avérés peu toxiques lors des tests de toxicité effectués sur des cellules eucaryotes hépatiques.

Keywords

Sugar lactones
α,β-Unsaturated carbonyl systems
Butenolides
Sugar enones
Thiosugars
Imino sugars
Wittig reaction
Ring expansion
Antibacterial activity
Antifungal activity

Palavras Chave / Mots Clés

Lactonas derivadas de açúcares	Lactones derivées de sucres
Sistemas carbonílicos α,β-insaturados	Systèmes carbonylés α,β-insaturés
Butenolidas	Butenolides
Enonas derivadas de açúcares	Énones derivées de sucres
Tioaçúcares	Thiosucres
Iminoaçúcares	Iminosucres
Reacção de Wittig	Réaction de Wittig
Expansão do anel	Expansion du cycle
Actividade antibacteriana	Activité antibactériènne
Actividade antifúngica	Activité antifongique

Abbreviations

AAPDH	2,2’-Azobis(2-amidinopropane) dihydrochloride
Ac	Acetyl
AD	Asymmetric dihydroxylation
AIBN	2,2'-Azobis(isobutyronitrile)
all	Allyl
APP	Ascopyrone P
aq.	Aqueous
ATCC	American Type Culture Collection
br.	Broad
Bn	Benzyl
Bz	Benzoyl
Boc	*tert*-Butoxycarbonyl
Cbz	Carboxybenzyl
CC	Column chromatography
CMC	Critical micellar concentration
CMG	Carboxymethyl glycoside
CMGL	Carboxymethyl glycoside lactone
COSY	Correlation spectroscopy
Cq	Quaternary carbon atom
CSA	Camphorsulfonic acid
d	Doublet
DCC	Dicyclohexylcarbodiimide
dd	Double doublet
ddd	Double double doublet
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless Enhancement by Polarization Transfer
DIBAL-H	Diisobutylaluminum hydride
Dig	Digitoxigenin
DMA	Dimethylaniline

DMAP	4-(Dimethylamino)pyridine
DMF	Dimethylformamide
DMJ	1-Deoxymannojirimycin
DNJ	Deoxynojirimycin
DMSO	Dimethyl sulfoxide
dq	Double quartet
dt	Double triplet
equiv.	Equivalents
ESR	Electron spin resonance
GABA	γ-Aminobutyric acid
GC-MS	Gas chromatography-mass spectroscopy
HMBC	Heteronuclear multiple-bond correlation
HMPA	Hexamethylphosphoramide
HMQC	Heteronuclear multiple-quantum correlation
HRMS	High resolution mass spectrometry
IBX	Iodoxybenzoic acid
isopr.	Isopropylidene
*i*Pr	Isopropyl
IR	Infra red
m	Multiplet
m-CPBA	*m*-Chloroperoxybenzoic acid
Me	Methyl
Ms	Mesyl (methanesulfonyl)
MW	Microwave irradiation
NBS	*N*-Bromosuccinimide
NBSH	*o*-Nitrobenzenesulfonyl hydrazide
NeuAc	*N*-Acetylneuraminic acid
NIS	*N*-Iodosuccinimide
NMO	*N*-Methylmorpholine *N*-oxide
NOESY	Nuclear Overhauser Effect Spectroscopy
Oct	Octoate (2-Ethylhexanoate)
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate

Pd/C	Palladium on charcoal
PG	Protecting group
Ph	Phenyl
Piv	Pivaloyl
PMPOH	*p*-Methoxyphenol
PPL	Porcine pancreatic lipase
ppm	Parts per million
py	Pyridine
q	Quartet
RCM	Ring-closing metathesis
room temp.	Room temperature
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDMS	*tert*-Butyldimethylsilyl
*t*Bu	*tert*-Butyl
td	Triple doublet
Tf	Triflyl (Trifluoromethanesulfonyl)
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*',*N*'-Tetramethyl-1,2-ethylenediamine
TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Ts	Tosyl (4-toluenesulfonyl)
UV	Ultraviolet

Table of Contents

1. Introduction

This PhD work was based on the synthesis and the use of carbohydrate bicyclic lactones for the access of sugar derivatives comprising an α,β-unsaturated carbonyl functionality, notably a butenolide moiety or an enone system. The motivation for the research on this type of compounds came from the known biological activity associated with the α,β-unsaturated carbonyl motif, which is frequently present in bioactive natural products. Their insertion in carbohydrates may thus provide potential bioactive substances. Moreover, taking into account the propensity of such conjugated systems to undergo a variety of reactions, these molecular targets may constitute functionalized chiral templates for derivatization. The biological activity of some of the synthesized molecules, namely the antimicrobial effect, was assessed.

The present manuscript is organized in subchapters which contain published papers achieved within the scope of this subject. The original work presented therein was developed and accomplished by the author of this thesis (N. M. Xavier) as well as the writing of the articles. When the article contains other co-authors besides the supervisors of this thesis, their role is specified at the beginning of each chapter.

Since sugar lactones constitute the key skeleton of the molecules investigated, as precursors or as final products, a general survey on carbohydrate-based lactones is given in the introduction, which was recently published in *Topics in Current Chemistry*. The thesis introduction, i.e. the state of art of the subject here explored, is therefore composed by the latter review along with the one published in *Carbohydrate Research*, covering the synthesis and usefulness of sugar derivatives containing α,β-unsaturated carbonyl systems, the target molecules of this PhD research work.

The results and discussion include the papers published on *Organic Letters* and on the *European Journal of Organic Chemistry* concerning the synthesis and biological activity of sugar-linked and sugar-fused butenolides and thiosugar bicyclic fused analogues. The paper concerning the exploitation of the methodologies previously developed towards imino sugar derivatives is already in press in the *European Journal of Organic Chemistry*. The last section, comprising a paper also in press in *Bioorganic & Medicinal Chemistry*, is dedicated to the use of carboxymethyl glycoside lactones as synthons for the preparation of sugar enones, conjugated diene pyranosides and related triazole-containing glycosides. Their antimicrobial evaluation was also performed.

In *General Conclusions*, the last chapter of this manuscript, a summary of the work developed in this PhD research program is presented. Emphasis is given on the efficacy of the synthetic methodologies developed, demonstrated by the variety of novel chemical targets which could be accessed, and on their interest from either chemical or biological point of vue.

1.1. Carbohydrate-Based Lactones

The following subchapter was published as:

"Carbohydrate-Based Lactones: Synthesis and Applications" Xavier, N. M.; Rauter, A. P.; Queneau, Y. *Topics Curr. Chem.* **2010**, *295*, 19–62.

and gives a general survey on the synthesis and uses of carbohydrate-based lactones. A special section gives emphasis to bicyclic systems, which is the type of compounds explored in this PhD work, as targets or as precursors, aiming at the insertion of α,β-unsaturated carbonyl systems in carbohydrate templates.

Topics Curr. Chem. **2010**, *295*, 19−62

Carbohydrate-Based Lactones: Synthesis and Applications

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Keywords: Aldonolactones / Bicyclic lactones / Gluconolactone / Sugar lactones / Synthons / Uronic acids

Abstract

The synthesis and uses of different kinds of carbohydrate-based lactones are described. This group of compounds includes aldonolactones, other related monocyclic lactones and bicyclic systems. The latter can arise from uronic acids, carboxymethyl ethers or glycosides, or from *C*-branched sugars.

Contents

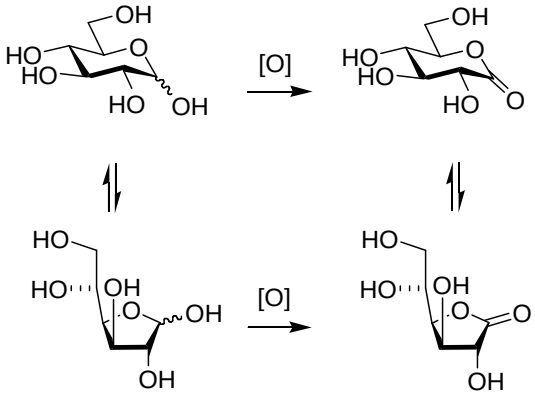
1. Introduction

Carbohydrate lactones have found broad applications as building blocks for the synthesis of important bioactive compounds and natural products, and constitute a valuable family of synthons for diverse types of transformations. Previous survey articles were published by De Lederkremer [1], Lundt [2–4] and Fleet [5]. In this revision, emphasis will be given to sustainable approaches involving a limited number of steps, to environmentally friendly synthetic methodologies for conversion of these molecules into functional compounds, and to multi-step sequences for the preparation of more complex targets. Starting with simple and available aldonolactones, the chemistry of more elaborated carbohydrate-based lactones, such as α,β-unsaturated δ-lactones as well as other types of bicyclic systems will then be presented and discussed. Allying the chirality inherent to the sugar to the reactivity of the lactone functionality turns these classes of compounds into useful chemical intermediates towards a variety of purposes.

2. Aldonolactone Synthesis

2.1. General Aspects

Aldonolactones are commercially avalailable at low cost, when compared to most of the common monosaccharides. They are typically synthesized by selective anomeric oxidation of unprotected aldoses with bromine [6]. Usually, the thermodynamically more stable five-membered lactone (γ-lactone) predominates over the six-membered form, with the exception of D-gluconolactone, which crystallizes as the 1,5-pyranolactone (δ-lactone) [17] (Scheme 1). Another method for the preparation of sugar lactones is the dehydrogenation of unprotected or partially protected alditols and aldoses catalyzed by a transition metal complex in the presence of a hydrogen acceptor [8–10]. Protected aldoses with a free anomeric hydroxyl group can be converted into the corresponding aldonolactones by common oxidation protocols, such as those employing chromium(VI) reagents [11] or DMSO-based oxidizing systems [12, 13]. Methods for aerobic oxidation of unprotected aldoses over heterogeneous catalysts, including Pd/C, Au/C or a combination of Bi-Pd/C, have also been developed [14–17]. However enzymatic processes for the synthesis of aldonolactones/aldonic acids are preferred on industrial scale.

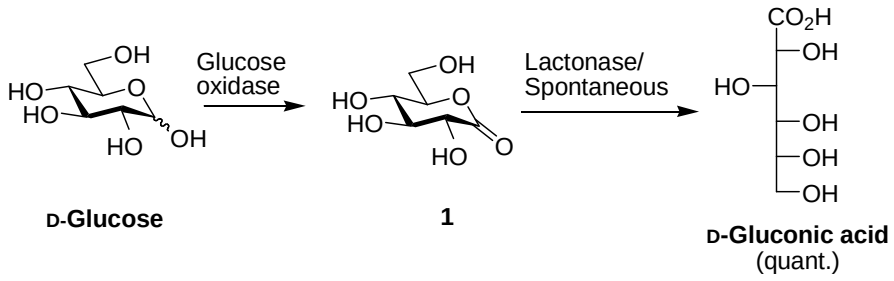


Scheme 1. Formation of 1,4 and 1,5-lactone from D-glucose.

2.2. Glucono-1,5-Lactone

Glucono-1,5-lactone (δ-D-gluconolactone, **1**) is the cyclic ester of D-gluconic acid, which is produced on the industrial scale by enzymatic oxidation of glucose (for a

review of the production, properties, and applications of gluconic acid and its derivatives see [18]). This process is mediated by enzymes from selected microorganisms, including bacteria such as *Pseudomonas* or *Gluconobacter oxydans* and fungi such as *Aspergillus niger*. The method involving *A. niger* is widely used and is based on glucose oxidase. The oxidation pathway consists in the oxidation of glucose to δ-D-gluconolactone, which is mediated by the latter enzyme, followed by hydrolysis to gluconic acid, which may occur spontaneously or be promoted by the lactonase enzyme (Scheme 2). After the fermentation process, the lactone can simply be recovered from the broth by crystallization. Under appropriate conditions, glucose can be quantitatively converted into gluconic acid. About 100 000 tons of D-gluconic acid, mainly used in food industry, are produced annually worldwide [19]. Glucono-1,5-lactone (**1**) has widespread application as a food additive, particularly in dairy products, confectionery, and meat.



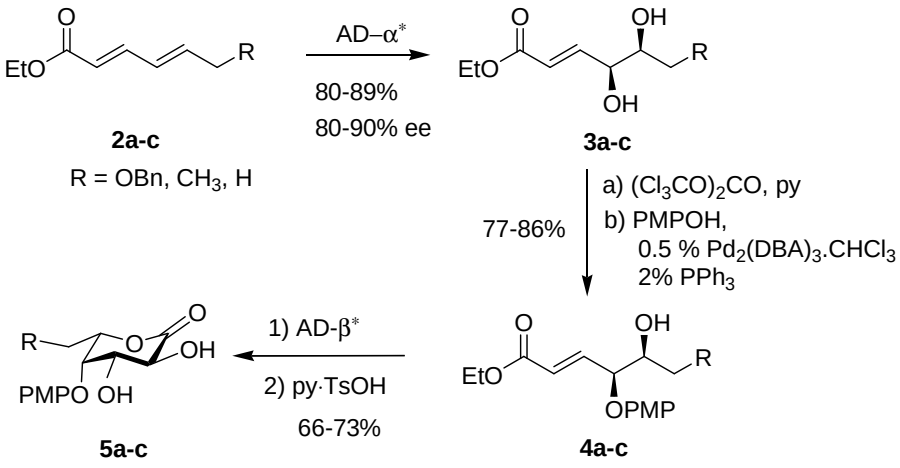
Scheme 2. Oxidation of D-glucose by *Aspergillus niger*.

2.3. Other Aldono-1,5-Lactones

Glycosyl azides have been shown to be useful precursors for the synthesis of aldonolactones. A viable one pot-procedure for the conversion of per-*O*-alkylated glycopyranosides into the corresponding aldono-1,5-lactones is based on the formation of glycosyl azide intermediates by treatment of the substrates with trimethylsilyl (TMS) azide in the presence of tin(IV) chloride, followed by hydrolysis [20]. In other work, aldono-1,4-lactones and aldono-1,5-lactones could be prepared from glycosyl azides via a two-step methodology consisting in the *N*-bromosuccinimide (NBS) mediated bromination and subsequent hydrolysis of corresponding *N*-bromoiminolactone intermediates [21].

Bierenstiel and Schlaf [22] were able to prepare and isolate for the first time the less stable δ-D-galactonolactone by oxidation of galactose with the Schvo's catalytic system, which is based on the dimeric ruthenium complex $[(C_4Ph_4CO)(CO)_2Ru]_2$. The transformation led to the δ-galactonolactone in 93% yield, against 7% of the isolated γ-lactone isomer. This procedure also allowed the preparation of δ-D-mannonolactone in a much better yield (94%) than that reported in an early procedure [23] based on crystallization from a solution of calcium mannonate in aq. oxalic acid.

O'Doherty and co-workers have explored the use of 2,4-dienoates as precursors for δ-galactonolactones [24, 25]. The synthetic approach involved sequential dihydroxylation steps of the dienoates (**2a**–**c**) double bonds by Sharpless AD-mix reagent systems (Scheme 3). After the first enantioselective dihydroxylation step, the resulting γ,δ-dihydroxyenoate intermediates (**3a**–**c**) were protected at the γ-hydroxyl group as cyclic carbonates, which were then treated with *p*-methoxyphenol (PMPOH) in the presence of a Pd(0) catalyst. The resulting 4-*O*-protected derivatives (**4a**–**c**) were submitted to diastereoselective dihydroxylation affording triols possessing *galacto* configuration, which were then lactonized to give the target L-galactono-1,5-lactones (**5a**–**c**) or their enantiomers, depending on the order in which the Sharpless reagents were applied [24].



AD–α* = 2% OsO4, 4% $(DHQ)_2PHAL$, 3 eq $K_3Fe(CN)_6$, 3 eq K_2CO_3, 1 eq $MeSO_2NH_2$
AD–β* = 2% OsO4, 4% $(DHQD)_2PHAL$, 3 eq $K_3Fe(CN)_6$, 3 eq K_2CO_3, 1 eq $MeSO_2NH_2$

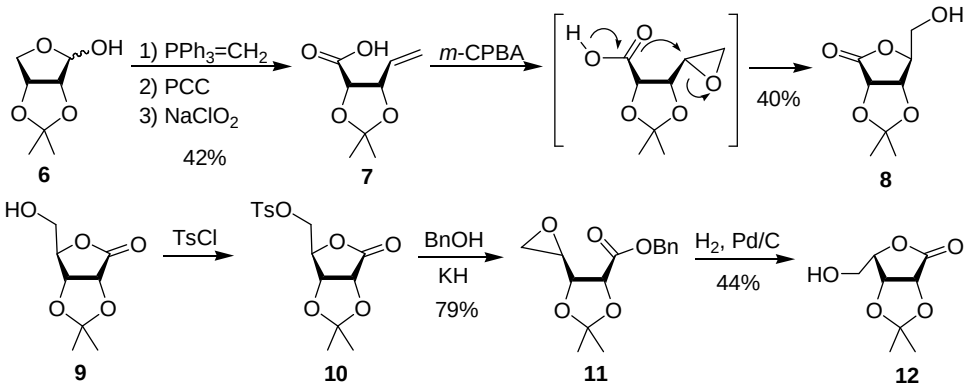
Scheme 3. Synthesis of L-galactono-1,5-lactones from 2,4-hexadienoates.

2.4. Aldono-1,4-Lactones

An efficient method for preparing aldono-1,4-lactones (γ-aldonolactones) as the single products from oxidation of unprotected or partially protected monosaccharides was reported [9]. It consisted in treatment of the latter by catalytic amounts of $[RuH_2(PPh_3)_4]$, in the presence of an excess of benzalacetone (*trans*-4-phenylbut-3-en-2-one) as the hydrogen acceptor, in DMF. The corresponding γ-lactones were obtained in excellent yields, even in the case of D-glucose, for which no 1,5-lactone was observed. The results suggested that the oxidation step is followed by a ring contraction mechanism, probably promoted by coordination of the catalyst to the endocyclic oxygen and to the carbonyl group, facilitating ring opening and its closure into the more thermodynamically stable five-membered form.

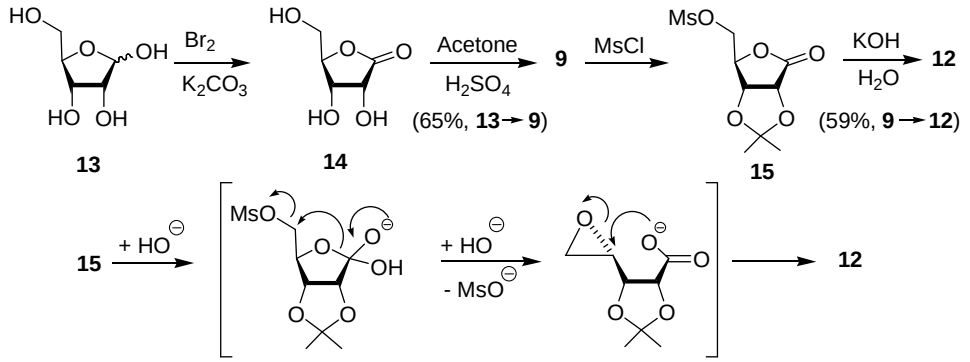
L-Aldonolactones are much less available than their D-enantiomers. Their potential to serve as chiral building blocks for L-sugar derivatives also makes them molecular targets of interest.

Stereoselective approaches involving few steps leading to 2,3-*O*-isopropylidene-L-ribonolactones and L-lyxono-1,4-lactones were reported by Rao and Lahiri [26]. The L-ribono derivative could be synthesized in three steps starting from the easily available isopropylidene-D-erythrose (**6**) (Scheme 4). It was converted into the unsaturated acid **7** by Wittig olefination and further oxidation. Epoxidation of the latter afforded the desired 1,4-lactone (**8**) in 40% yield, due to cyclization of the intermediate epoxide promoted by silica gel when attempting product separation by column chromatography. The synthesis of the L-lyxono-1,4-lactone derivative (**12**) was accomplished starting from D-ribono-1,4-lactone (**9**), of which 5-*O*-tosyl derivative **10** was treated with the potassium salt of benzyl alcohol to give the epoxy benzyl ester **11,** furnishing directly on catalytic hydrogenation the target compound in 44% yield.



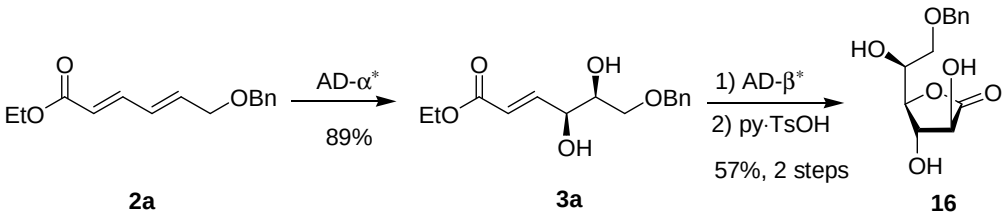
Scheme 4. Synthesis of 2,3-*O*-isopropylidene L-ribono- and L-lyxono-1,4-lactones.

More recently, a simple synthetic route for a large scale production of **12** (2,3-*O*-isopropylidene-L-lyxonolactone) was described [27]. The chosen starting material was D-ribose (**13**), which was oxidized to the corresponding lactone **14** (Scheme 5). The latter was submitted *in situ* to acetonation to provide the 2,3-*O*-isopropylidene derivative **9**, which was then mesylated at OH-5. Treatment of the crude 5-*O*-mesylate **15** with potassium hydroxide led to **12** according to the mechanism proposed in Scheme 5.



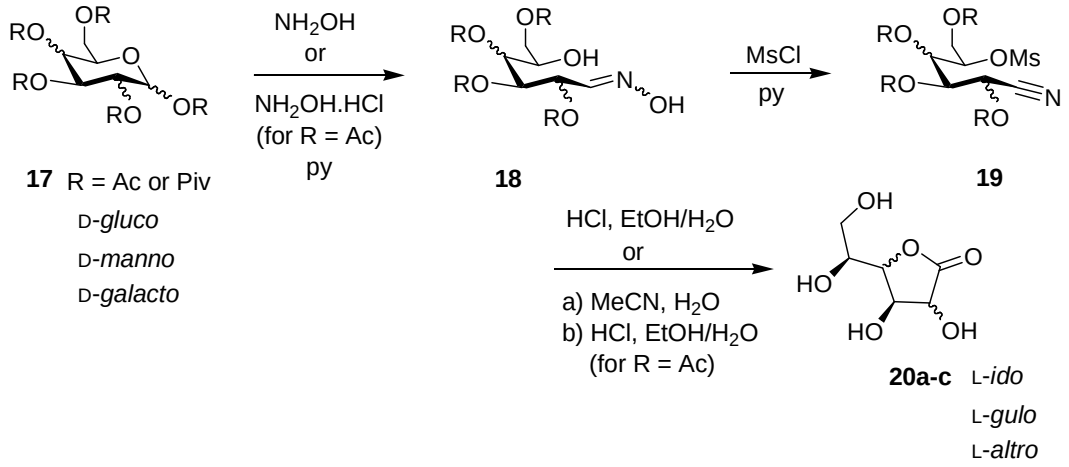
Scheme 5. Process for a large scale production of 2,3-*O*-isopropylidene L-lyxono-1,4-lactone.

L-Galactono-1,4-lactone (**16**) is prepared in three steps (51%, overall yield) from **2a** applying two successive asymmetric dihydroxylations (ADs) [25] (Scheme 6).



Scheme 6. L-Galactono-1,5-lactones from 2,4-hexadienoates.

L-Aldono-1,4-lactones can be prepared from D-aldose perpivaloates and peracetates (compounds of type **17**) [28]. The method implies formation of aldoximes (**18**), followed by mesylation (Scheme 7). The resulting 5-*O*-mesyl glyconitrile derivatives (**19**) are then submitted to acid-catalyzed hydrolysis giving the corresponding 1,4-lactones **20a–c**.



Scheme 7. L-Aldono-1,4-lactones from D-aldose perpivaloates and peracetates.

3. Aldonolactone as Useful Chirons

The use of aldonolactones for the preparation of carbasugars and iminosugars has been well explored and documented, particularly by Lundt's group [2–4, 29–31]. Fleet has also given an overview of the utility of sugar lactones as synthons for biologically active compounds [5] and his research group has made major contributions to the synthesis of sugar amino acids from aldonolactones [32–34]. We review here the syntheses of *C*-glycosyl compounds, L-sugars, imino- and thiosugars, natural products

and of surfactants and related polymers that make use of aldonolactones as starting materials.

As shown in chapter, "Synthetic polymers from readily available monosaccharides" by J.A. Galbis and M.G. Garcia-Martin,[1] aldonolactones are useful monomeric materials for the synthesis of biodegradable polymers and bio-compatible polymers for medicinal applications.

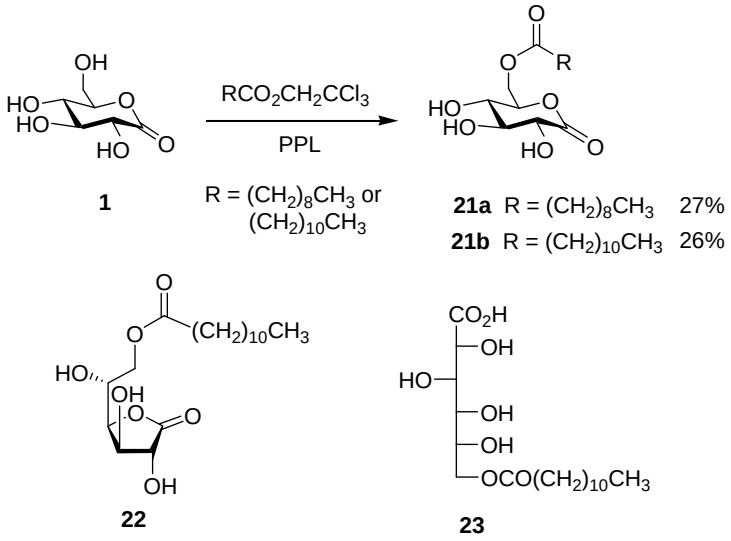
3.1. Synthesis of Surfactants and Polymers

Among the aldonolactone-based surfactants are aldonolactone-linked fatty esters which have been prepared by selective acylation of unprotected aldono-1,4-lactones or aldono-1,5-lactones. One of the first reported examples of this type of surfactants was applied to the enzymatic synthesis of 6-O-alkanoylgluconolactones [35]. Thus, 6-*O*-decanoyl- and 6-*O*-dodecanoyl- derivatives (**21a** and **21b**, respectively, Scheme 8) were obtained in 26–27% yield by esterification of glucono-l,5-1actone (**1**) at C-6 with the corresponding 2,2,2-trichloroethyl carboxylate in the presence of porcine pancreatic lipase (PPL) as catalyst. Compounds **21a**,**b** are soluble in water at 90–96 ºC but precipitate when cooled to 30–37 ºC. NMR and GC-MS analysis after dissolution and precipitation indicated the presence in the mixture of compound **21b**, the glucono-l,4-1actone-derived ester **22**, and the acyclic dodecanoylgluconic acid **23**, the latter being the major compound. This demonstrates that dissolution of **21b** occurs with hydrolysis of the lactone moiety giving a more soluble mixture of compounds that are more appropriate for detergent applications than the dodecanoylglucono-1,5-lactone itself.

Acylation of D-glucono-1,4- and D-glucono-1,5-lactone with *N*-(11-undecenoyl)-1,3-thiazolidine-2-thione in the presence of triethylamine gave 6-*O*-undecenoyl ester as the single product. In the case of the 1,5-lactone, isomerization to the 1,4-lactone-derived ester was observed, and quantitative conversion was attained when sodium hydride was used as base. In contrast with the expected regioselectivity at OH-6, acylation of L-galactono-1,4-lactone proceeded only at OH-2 although with a rather low yield (ca. 20%). Alternatively, the enzymatic route, employing *Candida antartica* and an ester,

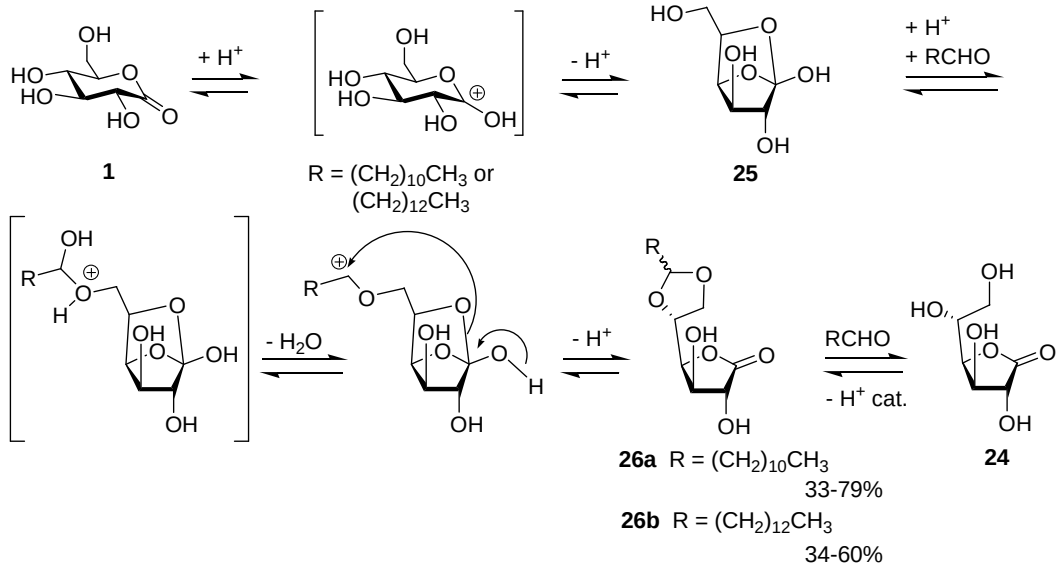
[1] *Topics Curr. Chem.* **2010**, *295*, 147–176.

proved to be more efficient, affording only 6-*O*-acylated-1,4-lactone derivatives in yields up to 76 and 85%, by acylation of D-glucono-1,5-lactone and L-galactono-1,4-lactone, respectively. The conversion was shown to increase with the electron-withdrawing character of the ester, while acids proved to be virtually unreactive as acylating agents [36].



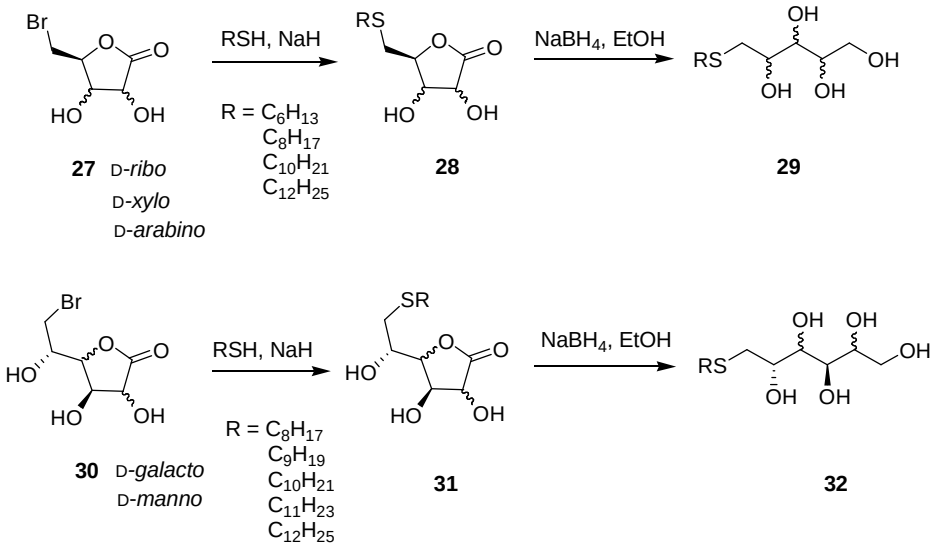
Scheme 8. Enzymatic synthesis of 6-*O*-alkanoylgluconolactones.

Another type of amphiphilic-like structure in which an aldonolactone moiety is present was prepared by acetalization of D-glucono-1,4-lactone (**24**) and D-glucono-1,5-lactone (**1**) with dodecanal or tetradecanal in the presence of methanesulfonic acid (Scheme 9) [37]. Both lactone isomers led to 1,4-lactone acetal derivatives **26a**,**b** in optimized yields up to 60–79%. A mechanism for the ring contraction was proposed, involving a hemi-orthoester (**25**) as a key intermediate in the addition to the aldehyde. Then, opening of an intermediate bicyclic-fused system and concomitant cyclization led to the acetal **26**.



Scheme 9. Acetalization of D-glucono-1,4- lactone and D-glucono-1,5-lactone with dodecanal or tetradecanal.

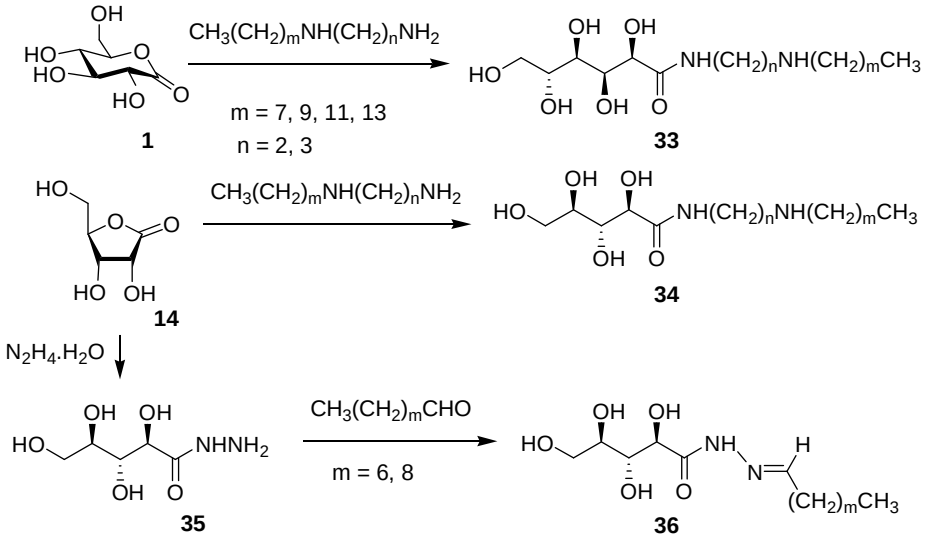
In the context of the synthesis of carbohydrate-based amphiphilic (alkylsulfanyl)polyols, Beaupère and co-workers explored the access to 5- and 6-alkylsulfanyl derivatives of pentono- and hexonolactones and their corresponding 1-(alkylsulfanyl)pentitols or 1- (alkylsulfanyl)hexitols [38, 39]. Bromolactones **27** and **30** were treated with alkanethiol in the presence of sodium hydride (Scheme 10) giving compounds **28** and **31**, respectively, in good yields (72–95%). Subsequent lactone reduction with $NaBH_4$ provided the 1-*S*-alkyl-1-thio-alditol derivatives **29** and **32**, respectively. Physico-chemical studies demonstrated surface activity for all compounds **28**, except for the D-ribono derivatives for which no critical micellar concentration (CMC) value was detected [40]. Apart from the lyxitol series, the pentitol derivatives of type **29** were shown to be more efficient in reducing the surface tension than their cyclic counterparts **28**. The mesophasic properties of **28** and **29** were also evaluated [41]. Most of the compounds gave lyotropic and thermotropic liquid crystals, except for the series of D-ribonolactones. This singular behavior for the *ribono* derivatives **28** was ascribed to the position of the vicinal hydroxyl groups which are in the same side of the cycle, favouring intramolecular hydrogen bonding.



Scheme 10. Amphiphilic (alkylsulfanyl)aldonolactones and corresponding alditols.

It has been known for more than fifty years that carbohydrate lactones undergo ring opening by amines. Using long chain primary amines gives access to amphiphilic structures that are emulsifying agents [42, 43] or liquid crystals [44–47]. The preparation of *N*-arylgluconoamides and *N*-alkylgluconoamides by opening of D-glucono-1,5-lactone, and their subsequent conversion into thiogluconamide derivatives, are reported [48]. Some amphiphilic alkyl aldonamides and diacetylenic aldonamides have the propensity to aggregate into supramolecular assemblies, leading to different structural morphologies [49–52]. Amphiphilic glycodendrimers containing aldonoamide moieties at their molecular surfaces have been prepared by coupling polyamine dendrimers with 1,5-D-glucono-1,4-lactone [53–55]. Such macromolecules are shown to behave as unimolecular micelles in water able to solubilize hydrophobic compounds in the dendritic cavities [55]. Highly enantioselective ketone reduction has been carried out in the presence of these systems.

In a recent work [56] aldonoamides (**33**, **34**) have been synthesized in moderate to good yields by addition of long-chain *N*-monoalkylated diamines to D-glucono-1,5-lactone **1** or D-ribono-1,4-lactone **14** (Scheme 11). In addition, hydrazones **36** have been obtained by treatment of the intermediate ribonohydrazide **35** with octanal or decanal. All compounds derived from ribonolactone showed moderate activity against *M. tuberculosis*. Some ribonoamides were also active against *Staphylococcus aureus*. The activities increased somewhat with the elongation of their hydrocarbon chains.



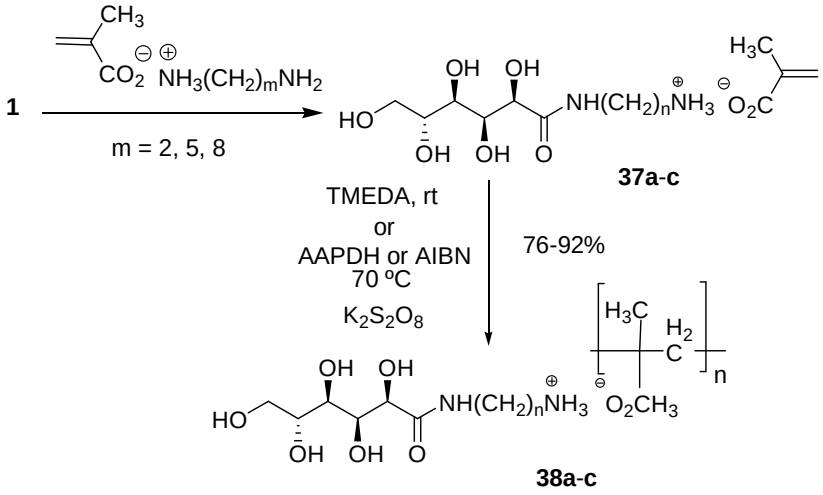
Scheme 11. Amphiphilic compounds by ring-opening of aldonolactones.

The use of carbohydrates as raw materials for the generation of polymers has attracted particular interest in the last two decades not only because of concerns related with sustainability and biocompatibility, but also due to the unique mechanical and physical properties that the sugar units may provide to the material [for reviews on carbohydrate-based polymers see [57–59]). The hydrophilic sugar moiety contributes to the specific three-dimensional structure of the polymer and increases its hydrophilicity and water solubility. Due to their particular characteristics, glycopolymers have found interesting applications as floculating agents, detergents, surface modifiers, and also in the biomedical field as biomaterials for tissue regeneration, as drugs and for gene delivery systems (See chapter, "From natural polysaccharides to materials for catalysis, adsorption and remediation", by F. Quignard, F. Di Renzo and E. Guibal,[2] and chapter, "Synthetic polymers from readily available monosaccharides", by J.A. Galbis and M.G. Garcia-Martin[1]).

One of the approaches employed to achieve sugar-based polymers consists in the preparation of monomers comprising the sugar moiety and a polymerizable double bond. Aldonolactones can be useful starting materials for this type of monomers, allowing the introduction of the polymerizable part through selective monofunctionalization of the lactone, without the use of protecting groups. The connection of both parts can be accomplished, for example, through amide linkages.

[2] *Topics Curr. Chem.* **2010**, *294*, 165–197.

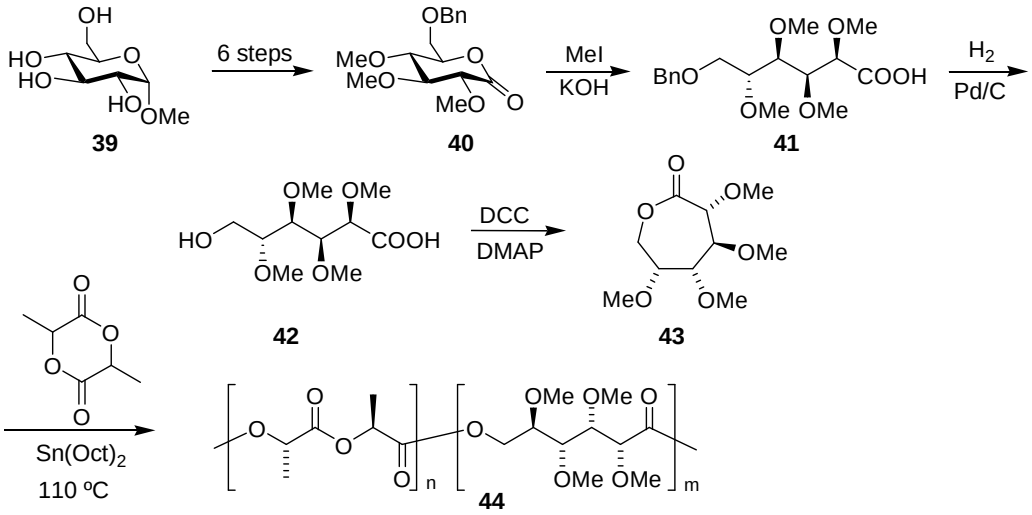
One of the first reported examples applying this approach [60] involved the addition of an aminoalkyl ammonium methacrylate salt, derived from a diamine and methacrylic acid, to D-glucono-1,5-lactone **1** (Scheme 12). The resulting ionic monomers **37** were then subjected to homopolymerization in the presence of a free-radical initiator to give the corresponding polymers **38** in good yields. Studies of the viscosity of their aqueous solution showed a decrease of this parameter when increasing the concentration, proving their polyelectrolyte nature. NMR analysis of polymers **38** revealed their predominant syndiotatic structure. The monomer **37a** (n = 2) was also copolymerized with 1-vinylpyrrolidin-2-one and methacrylamide, affording water-soluble copolymers.



Scheme 12. Gluconolactone-derived vinyl monomers and their polymerization.

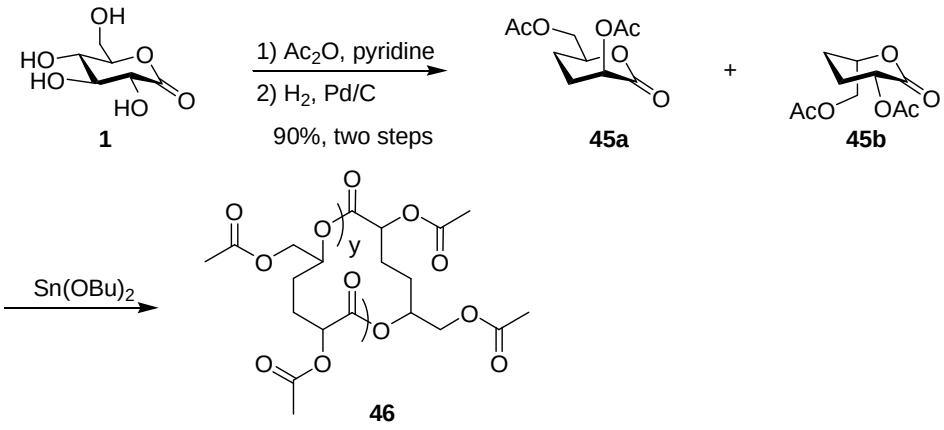
Aldonolactones serve as suitable monomers for the generation of homo- and copolymers, especially through ring-opening polymerization (ROP). Among them are the carbohydrate-analogues of ε-caprolactone, i.e. aldono-1,6-lactones. The first example of such derivatives and further ROP was reported by Galbis and co-workers [61] (See also chapter, "Synthetic polymers from readily available monosaccharides" by J.A. Galbis and M.G. Garcia-Martin[1]). Two alternative routes leading to tetra-*O*-methyl-D-glucono-1,6-lactone **43** were employed, one of them involving the intermediate protected glucono-1,5-lactone **40**, which was prepared from methyl D-glucopyranoside **39**. Opening of the lactone ring of **40,** methylation and hydrogenation led to the ω-hydroxygluconic acid derivative **42**, which was subsequently converted into **43** by lactonization (Scheme 13). Attempts to homopolymerize **43** failed. However, its

copolymerization by bulk ROP with L-lactide *Z*, using stannous octoate as initiator, provided two copolymers of type **44** containing up to 2.2% of the carbohydrate monomer.



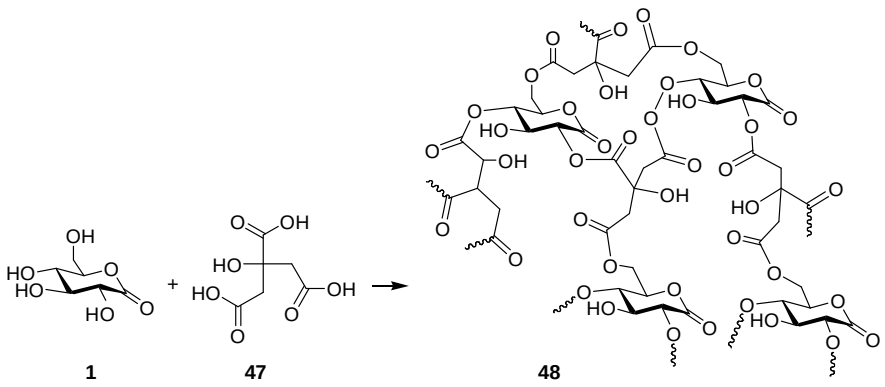
Scheme 13. Synthesis of a ω-hydroxygluconic acid from a protected glucono-1,5-lactone derivative and further copolymerization with L-lactide.

Williams and co-workers [62] have recently explored the ROP of acetylated aldono-1,5-lactones to investigate their propensity to oligomerize/polymerize by a metal alkoxide initiator. Hence, treatment of tetra-*O*-acetyl-D-glucono-1,5-lactone with 1,4-butanediol and stannous octanoate produced only a mixture of mono-, di-, and trialdaric esters. The latter were then subjected to copolymerization with [*R*,*S*]-lactide using an alkyl zinc initiator, which furnished triblock ABA copolyesters. Soon afterwards, the same group reported the ROP of 3,4-dideoxy-aldonolactones **45**, which were prepared in two steps from D-glucono-1,5-lactone (**1**) [63]. The polymerization was performed in the presence of $Sn(OBu)_2$, providing mainly cyclic polyesters **46** (Scheme 14).



Scheme 14. Ring-opening polymerization (ROP) of acetylated aldono-1,5-lactones.

An interesting type of polymeric network has been obtained by polymerization of D-gluconolactone (**1**) and citric acid (**47**) (Scheme 15) [64]. Instead of proceeding by a ROP mechanism, this polymerization was shown to occur through the esterification reaction between the hydroxyl groups of gluconolactone or citric acid and the carboxylic acid of citric acid, affording biodegradable cross-linked polyesters (**48**).

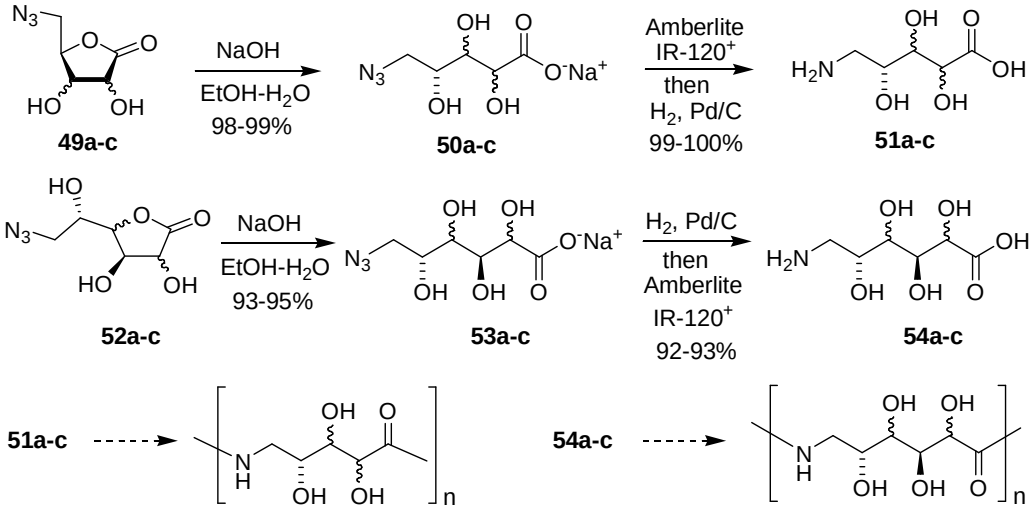


Scheme 15. Polymerization of D-gluconolactone and citric acid.

Polyhydroxypolyamides have attracted significant attention since they are more hydrophilic and biodegradable than nylons. Sugar amino acids [65] or aldaric acid derivatives [66, 67] are among the carbohydrate precursors that have been employed for the synthesis of these polyamides.

Simple syntheses of suitable monomers for nylon 5 and nylon 6 analogues, such as 5-amino-5-deoxy- and 6-amino-6-deoxyaldonic acids (**51**, **54**), have been achieved starting from unprotected D-pentono- and hexono-1,4-lactones [68, 69]. Saponification

of 5- or 6-azido-D-aldonolactones (*ribo*-, *arabino*-, *xylo*-, *galacto*-, *manno*-, compound types **49** and **52**) provided the corresponding 5- or 6-azido-aldonic acid sodium salts (**50** and **53**). A catalytic hydrogenation after or before treatment with acidic resin afforded compounds **51** and **54** in excellent overall yields (Scheme 16).



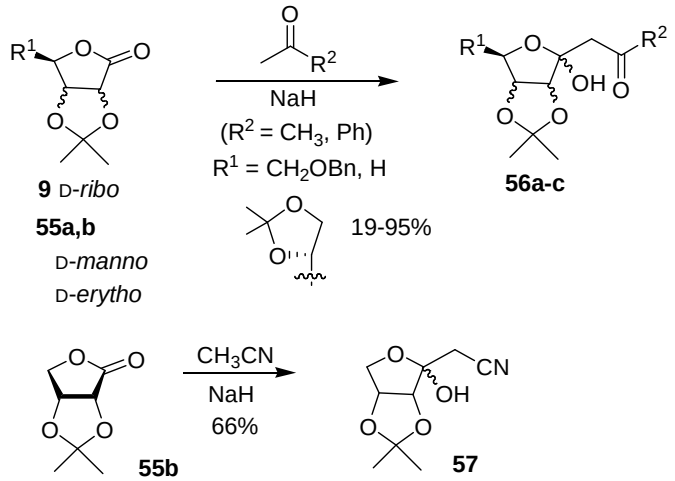
Scheme 16. Synthesis of 5-amino-6-deoxy- or 6-amino-6-deoxyaldonic acid monomers.

More recently, a similar synthetic strategy involving 2-azido-2-deoxy-D-xylono-1,4-lactone and 2-azido-2-deoxy-D-lyxono-1,4-lactone precursors has been applied for the synthesis of polyhydroxy α-amino acids, namely (–)-polyoxamic acid and 3,4-diepipolyoxamic acid [70].

Aldonolactone-based fluorinated surfactants have also been reported [71].

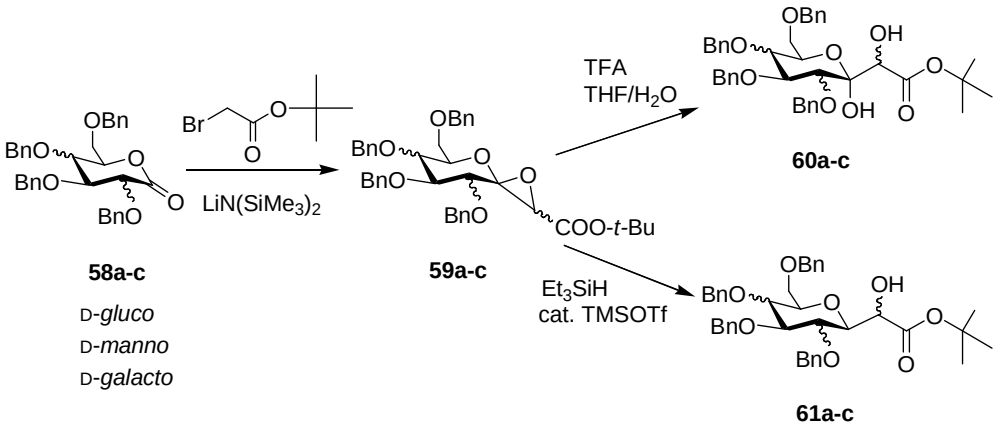
3.2. Synthesis of *C*-Glycosyl Compounds

C-Glycosyl compounds are important molecular targets as they occur in Nature and have interesting biological properties (for reviews on C-glycosylation, see [72–75]). Chain extensions of aldonolactones have been employed to create C-C bond formation at the anomeric center. Claisen-type reactions of aldono-1,4-lactones (e.g., **9**, **55**) with acetone or acetophenone (Scheme 17) generate hemiacetals of type **56a**–**c** [76]. Similarly, lactone, **55b** reacts with CH_3CN/NaH to give hemiacetal **57**.



Scheme 17. C-Glycosylation by Claisen-type reaction of aldono-1,4-lactones with acetone, acetophenone, or acetonitrile.

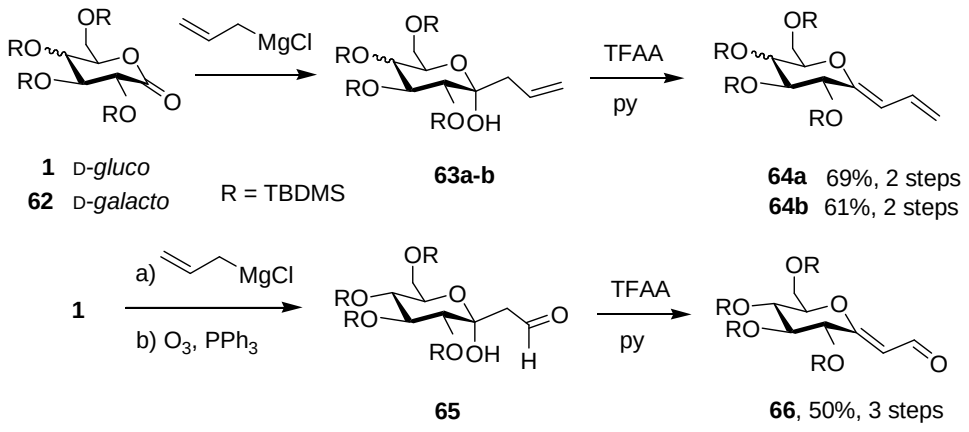
Using the enolate of *tert*-butyl bromoacetate with 1,5-lactones **58** (Scheme 18) led directly to exocyclic epoxides **59**, which were subsequently transformed into *C*-ketosides **60** [77]. Alternatively, cationic reduction of epoxides **59a–c** provided *C*-glycosyl compounds **61a–c**. Upon esterification of the latter as trifluomethanesulfonates, reaction with primary amines furnished the corresponding *C*-glycosylamino esters.



Scheme 18. Claisen condensation of aldono-1,5-lactones leading to exocyclic epoxides and further conversion into *C*-glycosyl derivatives.

Olefination of protected aldonolactones is a convenient approach to *C*-glycosylation that furnishes *C*-glycosylidene derivatives, often referred as "*exo*-glycals" [78]. Activated olefins, such as 1-*C*-dichloromethylene [79], 1-*C*-methoxycarbonylmethylene [80] and 1-*C*-cyanomethylene derivatives [81] have been obtained by direct Wittig-type olefination of aldonolactones. Hydrogenation of the *C*-glycosylidene compounds produces the corresponding *C*-glycosyl derivatives with high stereocontrol. However, *exo*-glycals resulting from partially protected aldonolactones, and that possess free hydroxyl groups appropriately located in the sugar ring, were shown to undergo 1,4-addition within the activated double bond to give bicyclic derivatives [82]. This propensity for activated *exo*-glycals to act as Michael acceptors permits the synthesis of *N*-glycosyl β-amino esters through stereoselective 1,4-addition of benzylamine, followed by reduction [83]. The latter compounds can be manipulated as standard amino acids and can enter into peptide synthesis. The synthesis of a variety of tri- and tetrasubstituted *exo*-glycals was accomplished from tetra-*O*-benzyl-D-glucono-1,5-lactone applying a modified Julia olefination procedure [84].

Another method for the alkylidenation of aldonolactones uses additions of organometallic reagents [78]. For example, Lin et al. [85] described an efficient route to conjugated anomeric dienes (**64a**,**b**) or aldehydes (**66**) based on the reaction of aldono-1,4- and 1,5-lactones (**1**, **62**) with allylmagnesium chloride (Scheme 19), giving allyl hemiacetals (e.g.: **63a**,**b**). Hemiacetal can be dehydrated [e.g.: with $(CF_3CO)_2O$] to produce dienes **64a**,**b**, or ozonolyzed (e.g. to give **65**).



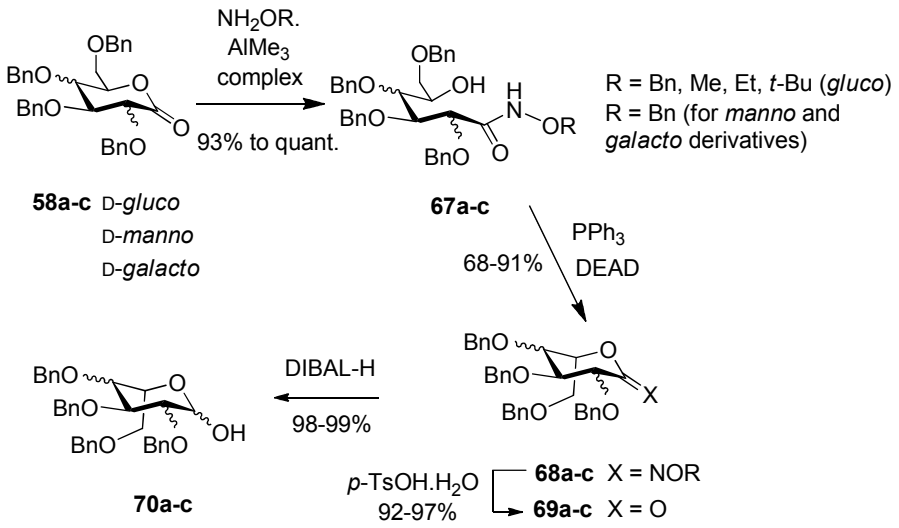
Scheme 19. *C*-Glycosyl derivatives by addition of allylmagnesium chloride to aldonolactones.

C-Glycosyl aromatic compounds are particularly relevant owing to their presence in a variety of biologically important natural products, including antibiotics (for reviews concerning the synthesis and biological profile of *C*-glycosyl aromatic compounds, see [86–89]). Based on the method of Sulikowski and co-workers [90], Li et al. [91] developed an efficient one-pot procedure for the synthesis of a series of *C*-aryl glycals in 75–92% yields. It consisted in the addition of aryllithium reagents to variously protected 2-deoxy-aldono-1,5-lactones, followed by treatment with a mixture of pyridine (py), 4-dimethylaminopyridine (DMAP), and trifluoroacetic anhydride (TFAA).

3.3. Synthesis of L-Aldoses

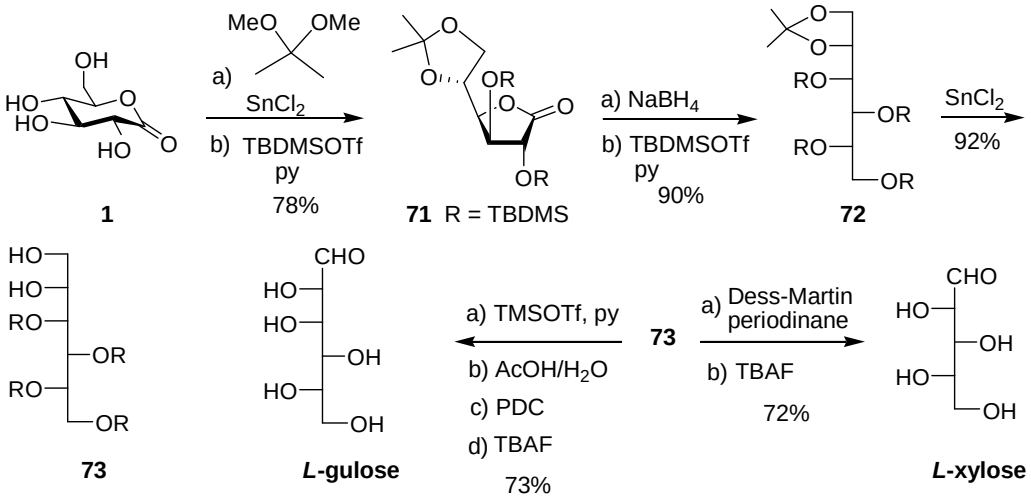
L-aldoses are scarcely available from natural resources. However, their utility as building blocks for natural products and analogues has prompted the search for efficient methods for their synthesis. Lipták and co-workers [92] have prepared L-glucose through standard manipulations starting from D-gulono-1,4-lactone. The synthetic pathway included conversion of the lactone into 1,2,3,4,5-penta-*O*-benzyl-D-gulitol, 1,2,3,4,5-penta-acetyl-D-gulitol, or 1,2,3,4,5-penta-benzoyl-D-gulitol, oxidation at C-6 to the corresponding aldehydes, and further deprotection with concomitant pyranose ring closure. Yields in L-glucose ranged from 34 to 53% overall yield, the best one being obtained from the penta-*O*-acetyl-D-gulitol derivative.

A general and effective four-step procedure for the conversion of D-hexono-1,5-lactones into L-hexoses was developed [93]. It involved alkoxyamination of tetra-*O*-benzyl-aldono-1,5-lactones **58a**–**c** mediated by $AlMe_3$ to provide the corresponding δ-hydroxyalkoxamates **67a–c**, which were then engaged into an intramolecular cyclization under Mitsunobu displacement conditions (Scheme 20). This cyclization occurred mainly via *O*-alkylation, affording the corresponding oxime derivatives **68a–c** in good yields, all with the expected inversion of configuration at C-5. At this stage, the acid-catalyzed hydrolysis of the oximes to the parent L-glycono-1,5-lactones **69a–c** provided, after reduction with diisobutylaluminum hydride (DIBAL-H), the corresponding tetra-*O*-benzyl-L-hexoses **70a–c**.



Scheme 20. Conversion of D-hexono-1,5-lactones into L-hexoses via δ-hydroxyalkoxamate derivatives.

A relatively short route has been presented to convert D-glucono-1,5-lactone (**1**) into L-xylose and L-gulose [94] (Scheme 21). Acetalization of **1** gave **71**, the reduction of which with $NaBH_4$ and subsequent silylation afforded **72**. Deacetylation with $SnCl_2$ gave **73** which was converted either into L-gulose or L-xylose applying standard reactions.

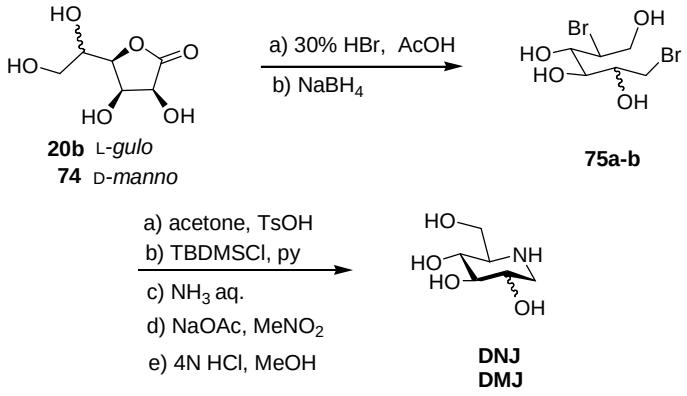


Scheme 21. Synthesis of L-aldoses from D-glucono-1,5-lactone.

3.4. Synthesis of Iminoalditols and Analogues

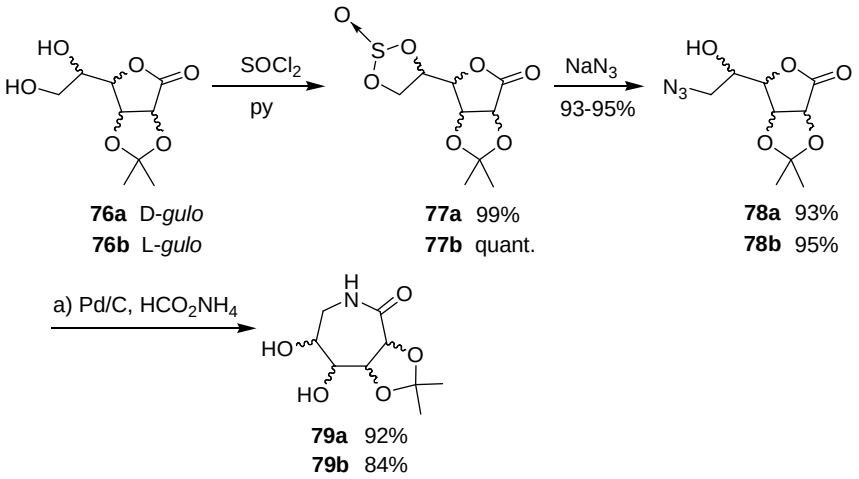
Imino sugars (or imino-dideoxyalditols) are alditols in which the ring ethereal moiety has been replaced by an amino group. These sugar mimetics are potential therapeutic agents, particularly due to their ability to act as glycosidase inhibitors [95]. Among them are found the naturally occurring 1-deoxynojirimycin (DNJ) and 1-deoxymannojirimycin (DMJ) [96].

Practical syntheses of DNJ and DMJ start from L-gulono-1,4-lactone (**20b**) and D-mannono-1,4-lactone (**74**), respectively [97]. Key intermediates are 2,6-dibromo-2,6-dideoxy-D-alditol derivatives **75a** and **75b** obtained by 2,6-dibromination of the starting lactones, followed by reduction with $NaBH_4$ [98, 99]. Then a five-step sequence involving selective partial protection, introduction of an amine functionality, and intramolecular *N*-alkylation, lead to DNJ and DMJ, respectively (Scheme 22).



Scheme 22. Synthesis of 1-deoxynojirimycin (DNJ) and 1-deoxymannojirimycin (DMJ).

Related imino alditols such as azepanes or lactam derivatives have been obtained and have shown to be glycosidase inhibitors [96, 100]. Both D- and L-gulonolactone have been converted into polyhydroxylated 1,6-aldonolactams of type **79** in a sequence of straightforward functional transformations, including sulfinylation of the corresponding aldonolactone-derived acetonides **76** that gave 5,6-cyclic sulfites **77** (Scheme 23) [101]. The latter reacted with sodium azide giving 6-azido derivatives **78**. In situ reduction of **78** and *N*-cyclization led to the targeted azepanes **79**.

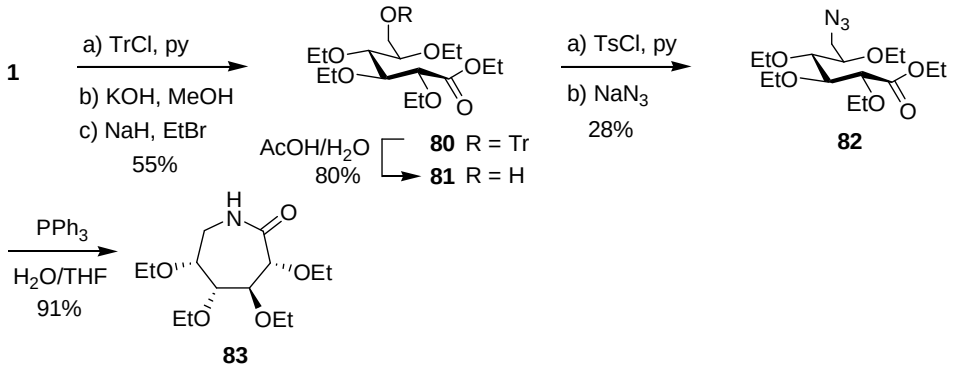


76a D-*gulo* **77a** 99% **78a** 93%
76b L-*gulo* **77b** quant. **78b** 95%

79a 92%
79b 84%

Scheme 23. Synthesis of di-hydroxylated 1,6-aldonolactams via aldonolactone-derived sulfites.

A concise synthesis of tetra-*O*-ethyl aldonolactam **83** starting from **1** has been reported [102]. After protection of its primary alcoholic moiety as a trityl ether, saponification and treatment with EtBr generated **80**. Acidic hydrolysis liberated **81** that was esterified (tosylate). The latter was displaced with NaN_3 to give azide **82**. Reduction of **82** resulted in lactam **83** (Scheme 24).



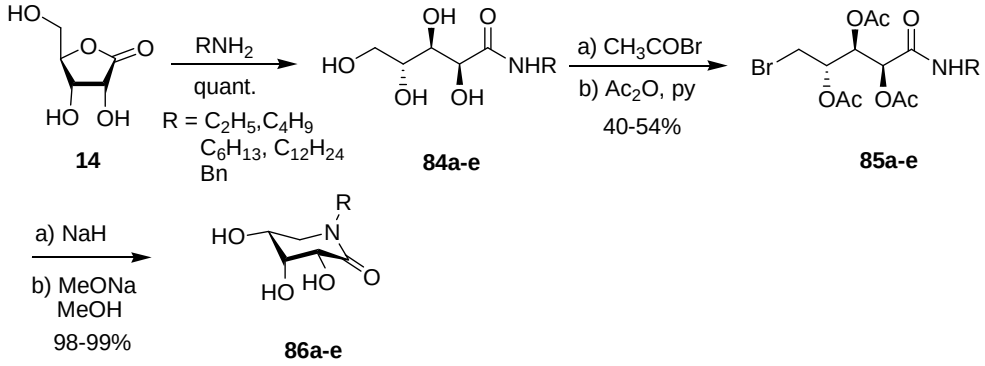
82

83

Scheme 24. Synthesis of a tetra-*O*-ethylaldonolactam from D-glucono-1,5-lactone.

Quite often *N*-alkylated imino sugars exhibit stronger glycosidase inhibitory activity than the corresponding non-alkylated derivatives [96, 103]. The synthesis of a series of hydroxylated *N*-alkyl aldonolactam derivatives was recently accomplished in a four-step sequence and good overall yields starting from D-ribono-1,4-lactone (**14**) [104]. Treatment of **14** with primary amines, and subsequent selective bromination of the

resulting amides **84** and acetylation, provided the corresponding bromoamide derivatives **85**. The latter were then submitted to intramolecular cyclization to afford the corresponding *N*-alkyl ribonolactams, the transmethanolyse of which led to the final compounds **86** (Scheme 25).

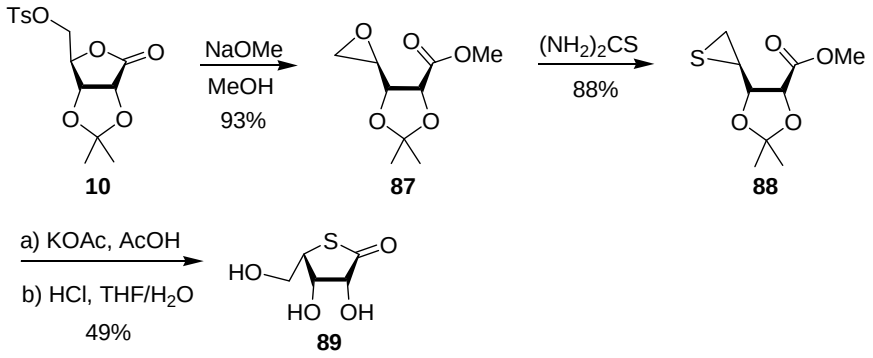


Scheme 25. Synthesis of a *N*-alkylated aldonolactam from ribono-1,4-lactone.

3.5. Synthesis of Thiosugars

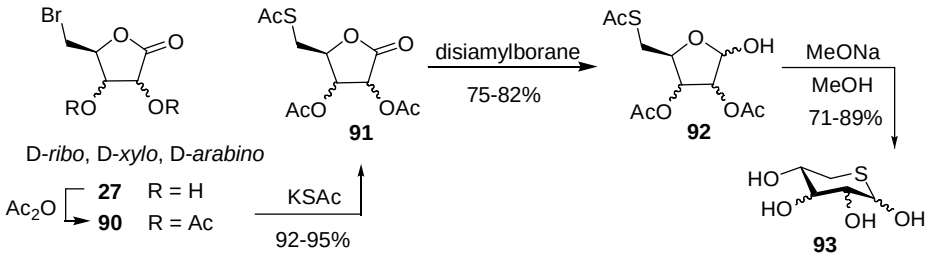
Thiosugars constitute another class of carbohydrate analogues presenting interesting biological and pharmacological properties [105, 106].

4-Thio-L-lyxono-1,4-lactone (**89**) has been prepared starting from 2,3-*O*-isopropylidene-5-*O*-tosyl-D-ribonolactone (**10**, D-*ribo*). **10** was converted first into epoxide **87** (Scheme 26) and then into episulfide **88** on treatment with thiourea. Regioselective opening of the thiirane ring of **88** and simultaneous lactonization, followed by removal of the protecting groups, furnished enantiomerically pure **89**. A similar synthetic pathway was employed for the synthesis of 4-thio-D-ribono-1,4-lactone starting from D-gulono-1,4-lactone [104].



Scheme 26. Synthesis of 4-thio-L-lyxono-1,4-lactone from 2,3-*O*-isopropylidene-5-*O*-tosyl-D-ribonolactone.

Beaupère and co-workers have proposed a short synthesis of 5-thio-D-pentopyranoses **93** applying a sequence of simple reactions starting from 5-bromopentono-1,4-lactones of type **27** (Scheme 27) [108, 109]. The latter were acetylated and subsequently converted into their corresponding 5-*S*-acetyl-5-thio derivatives **91**. Reduction of **91** into lactols **92** was followed by deprotection, furnishing the desired pentose derivatives **93** in good overall yields.



Scheme 27. Synthesis of thio-D-pentopyranoses from 5-bromo-D-pentono-1,4-lactones.

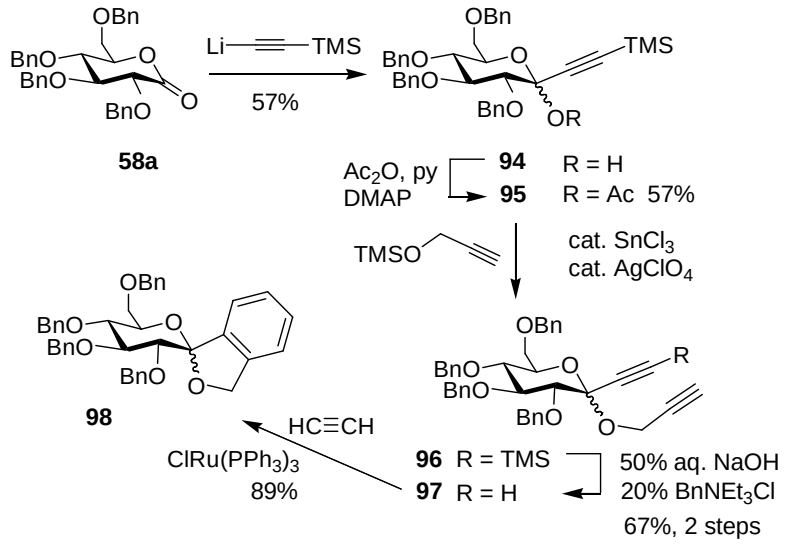
3.6. Synthesis of Bioactive Natural Products

Selected examples of the synthesis of natural products starting from aldonolactones are presented in this section.

Spirocyclic *C*-aryl glycosides are central structural skeletons of papulacandins that constitute a family of novel antifungal antibiotics isolated from a strain of *Papularia*

sphaerosperna. They have shown potent in vitro antifungal activity against *Candida albicans*, *Candida tropicalis*, *Pneumocystis carinii*, among other microorganisms [110].

One route to spirocyclic *C*-glycosyl aromatic compounds is based on the addition of functionalized organolithium reagents to D-glucono-1,5-lactone (for example [111–113]). For instance addition of 2-(trimethylsily1)ethynyllithium to tetra-*O*-benzyl-D-glucono-1,5-lactone (**58a**) gave the hemiacetalic 1-*C*-ethynyl derivative **94** as an anomeric mixture (Scheme 28). Acetylation of the tertiary hydroxyl group was followed by Lewis acid-mediated propargylation to give diyne **96**. Desilylation of **96** followed by cyclotrimerization in the presence of Wilkinson's catalyst gave the desired spiroketal core **98** in 89% yield.

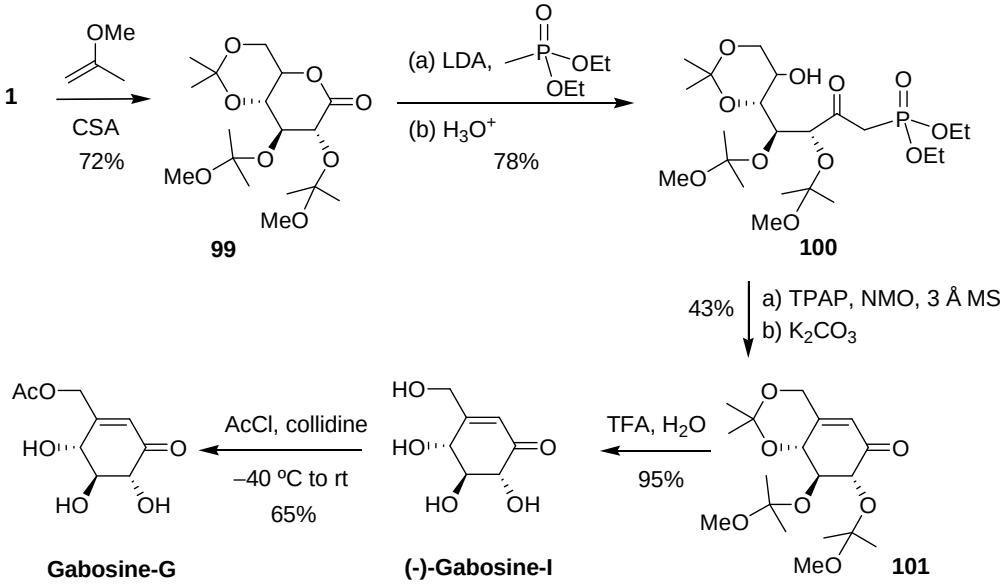


Scheme 28. Synthesis of a spirocyclic *C*-aryl glycoside from tetra-*O*-benzyl-D-glucono-1,5-lactone.

Spirocyclic *C*-ribosyl aromatic compounds have also been derived from D-ribono-1,4-lactone by a similar strategy. In this case a mild cylopentadienyl ruthenium complex was used as catalyst for the cycloaddition step [114].

Gabosines which have been isolated from *Streptomyces* strains constitute a family of keto carbasugars, most of them possessing a trihydroxylated cyclohexenone structure. Because of their interesting bioactivities, a large number of synthetic approaches to these compounds have been proposed (for example [115, 116]).

The shortest route (four to five steps) to gabosines I and G was accomplished starting from D-glucono-1,5-lactone (Scheme 29) [117]. Thus, acetalization of **1** with 2-methoxypropene resulted in the mixed acetal derivative **99** which underwent nucleophilic addition by the anion of diethyl methylphosphonate to afford the β-ketophosphonate **100**. The latter compound was subsequently submitted to a one-pot tetrapropylammonium perruthenate (TPAP) oxidation/K_2CO_3-mediated intramolecular Horner-Wadsworth-Emmons olefination, providing enone **101** in 43% yield. Other oxidation/cyclization conditions were less efficient. Deprotection of **101** furnished (–)-gabosine I which, in turn, could be acetylated regioselectively to give gabosine G.



Scheme 29. Synthesis of (–)-gabosine I and gabosine G from D-glucono-1,5-lactone.

3.7. α,β-Unsaturated Aldonolactones

Sugar-based lactones comprising an α,β-unsaturation are carbohydrate chiral building blocks with biological potential. Rauter and co-workers have reported the first synthesis of α,β-unsaturated lactones linked/fused to sugars and the field was broadly covered in a recent review [118–120]. Concerning monocyclic derivatives, i.e., α,β-unsaturated aldonolactones, a readily available 2,3-unsaturated aldonolactone is L-ascorbic acid (Vitamin C). Its chemistry and usefulness as chiral synthon has been reviewed very

recently [121]. It is a versatile starting material for the synthesis of L-hexoses [122, 123].

Both aldono-1,4-lactones and aldono-1,5-lactones have the tendency to undergo β-elimination on acylation to give butenolides or pyranoid α,β-unsaturated aldonolactones, respectively [1]. 2,3-Unsaturated aldono-1,4-lactones are also easily obtained from 2-bromo-2-deoxyaldono-1,4-lactones through a mild reductive elimination of the C-2 bromine and a *trans*-vicinal acetoxy group that uses sodium sulfite in methanol [124,125]. 2-Deoxysugar lactones are intermediates for ulosonic acids [126–128].

Most of the methodologies applied to prepare pyranoid α,β-unsaturated lactones start with glycals [129–132]. The Lichtentaler's group developed a one-pot procedure consisting in the oxidation of glycals and 2-acyloxyglycal esters with *m*-chloroperbenzoic acid in the presence of boron trifluoride etherate [133–136]. Another major contribution to this field was realized by Chmielewski and co-workers. Their method was based on the oxidation of protected glycals with hydrogen peroxide in the presence of molybdenum trioxide catalyst to the corresponding anomeric hydroperoxides, which could then be readily converted into the pyranoid unsaturated lactones on treatment with Ac_2O/py [137–140]. This group has explored the ability of sugar-based α,β-unsaturated lactones to react as Michael acceptors or as dipolarophiles in cycloaddition reactions, for the synthesis of important molecular targets, including imino sugars and natural compounds of biological interest (for example [141–146]).

4. Bicyclic Carbohydrate-Based Lactones

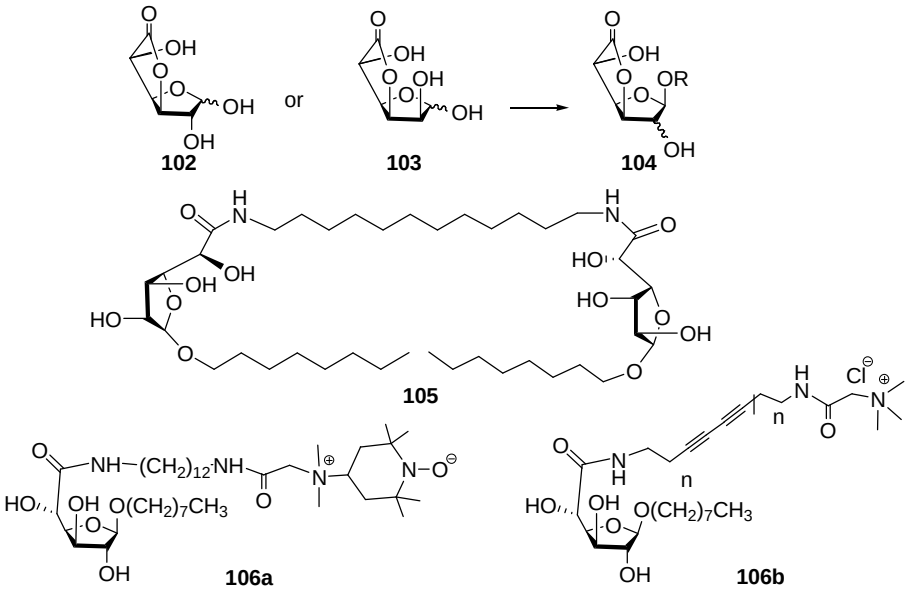
Bicyclic carbohydrate-based lactones can be divided into three classes: (1) lactones involving a carboxy group present on the sugar moiety (uronic and sialic acid lactones), (2) lactones involving a carboxy group formed by derivatization of a sugar hydroxyl group (carboxyalkyl ethers and glycosides), and (3) lactones involving a carboxy group present on a *C*-branched appendage.

When the lactone function of such bicyclic systems is consumed in a ring opening reaction, the main carbohydrate cyclic backbone is maintained in the product, unlike aldonolactones. Selected recent examples will be given in this section.

4.1. Uronic Acid Derived Lactones

The occurrence of uronic acid provides another means of easy access to bicyclic lactones, which can be used for the synthesis of various targets, such as surfactants or pseudo glycopeptides.

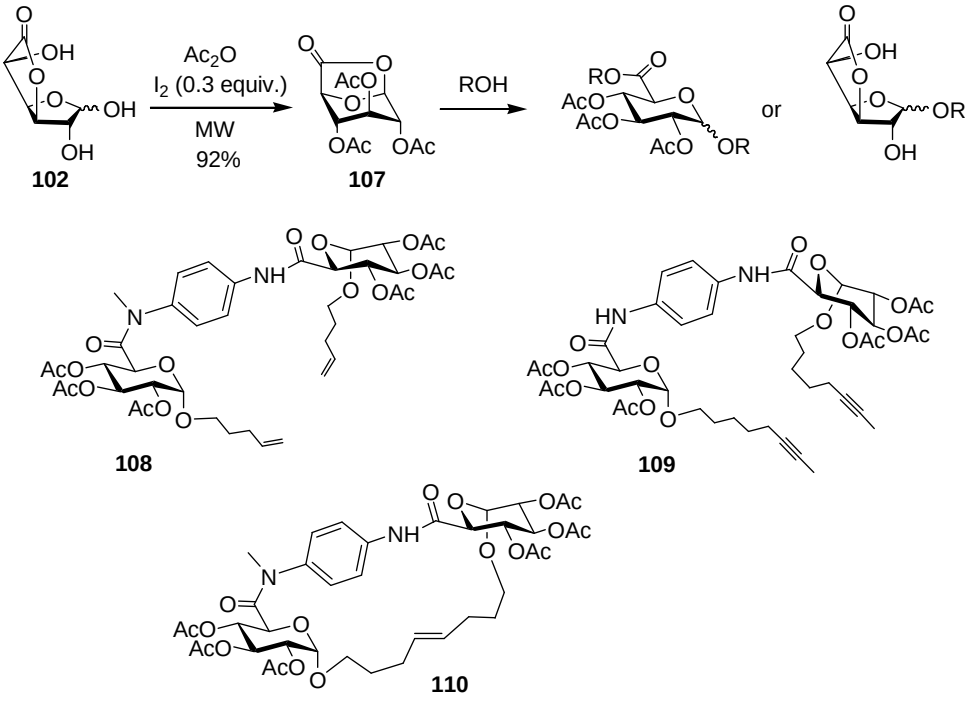
Alkyl furanosides can be obtained stereoselectively from the readily available D-glucofuranurono-6,3-lactone **102** arising from D-glucuronic acid, or from D-mannofuranurono-6,3-lactone **103**, which is obtained by acidic hydrolysis of alginic acid (Scheme 30) [147–149]. The lactone function of alkyl glucosides **104** can be opened by amines leading to new amphiphilic derivatives [42]. Pseudo macrocyclic bola-amphiphiles **105** are accessible by treatment of the lactone with a long-chain diamine [150]. Selective monoacylation of diamines can be followed by functionalization of the second amino group with different functional moieties, such as a nitroxide for ESR (electron spin resonance) studies (e.g., **106a**) or a cationic glycine betaine for making bolaphiles (e.g., **106b**).



Scheme 30. Bolaphiles derived from uronic acid 3,6-lactones.

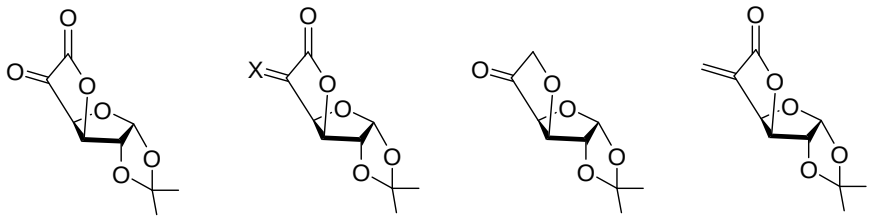
Variations of the self-assembly properties of the latter compound was studied as a function of the length and nature of the alkyl chain spacer connecting both polar heads [151–153].

If the anomeric hydroxyl group is involved in the lactone ring (6,1-lactones) such as in compound **107**, the lactone is rapidly opened in the presence of a Lewis acid (Scheme 31). As in Hoffmann's systems arising from [4+3] cycloaddition methodology [154, 155], such lactones can be seen as tethered anomeric acetates acting as intramolecular leaving groups. Stereoselective glycosylations can thus be achieved with different selectivities depending on the nature of the substituent at C-2 and on the reaction conditions [catalyst, microwave irradiation (MW)]. In some cases, concomitant esterification of the released carboxylic acid is observed (Scheme 31) [156–158]. When the released carboxylic group reacts with diamines, more elaborated systems such as dienes **108** or diynes **109** can be obtained and used in subsequent intramolecular ring-closing metathesis to form glycophanes such as compound **110** [159].



Scheme 31. Opening of glucuronic acid 6,1-lactone.

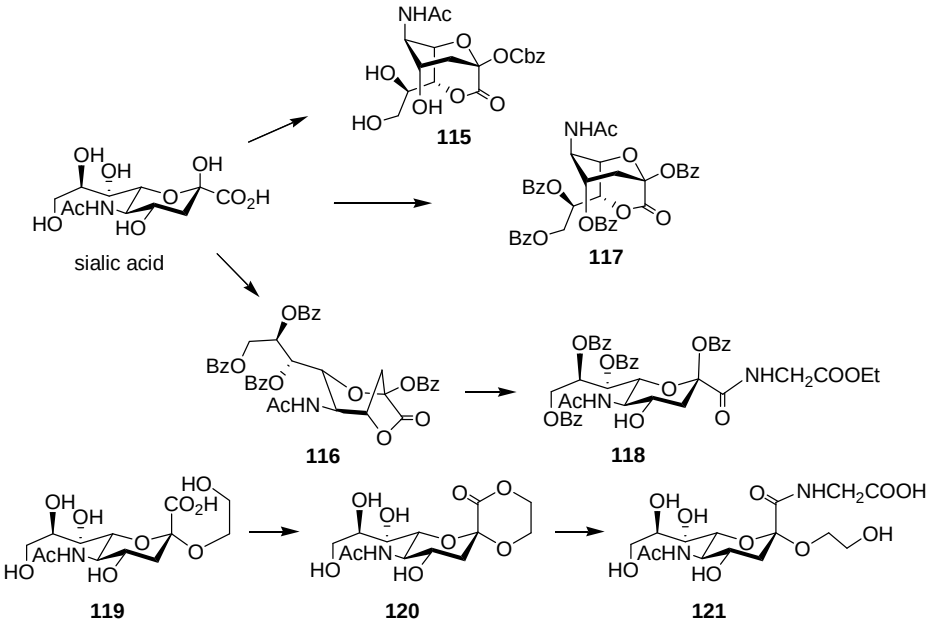
Rauter and co-workers demonstrated that C-5-alkylidene derivatives **112** of D-hexofuranurono-6,3-lactone can be obtained by Wittig olefination of the α-ketolactone **111** [160]. The related α-methylene lactone **114** was prepared in three steps from 3,6-anhydro-1,2-*O*-isopropylidene-α-D-*xylo*-5-hexulofuranose **113** via Wittig reaction and allylic oxidation.



Scheme 32. Alkylidene derivatives of glucuronic acid 6,3-lactone.

In a similar manner, sialic acids are liable to lactone formation. In some cases the observed lactones have been suggested to possess enhanced biological properties with respect to the corresponding open hydroxyacids [161–163]. Sialic acid 1,7-lactone **115** is readily obtained [164]. It is present in many glycoproteins [165, 166].

Under various acetylation conditions, sialic acid leads to either 1,4-lactone **116** or to the 1,7-lactone **117** depending upon the equatorial or axial orientation of the carboxyl group (Scheme 33). In the presence of a more hindered acylating agent, e.g., CbzCl (benzyl chloroformate), an activated acyl intermediate can be formed and quantitative chemoselective 1,7-ring closure into compound **115** has been observed. Lactone **116**, as well as lactone **120** arising from the glycol glycoside **119**, were suggested to be the intermediates in the formation of NeuAc-aminoacid hybrids **117** and **121**. These compounds were designed as potential sialidase inhibitors [161, 167].

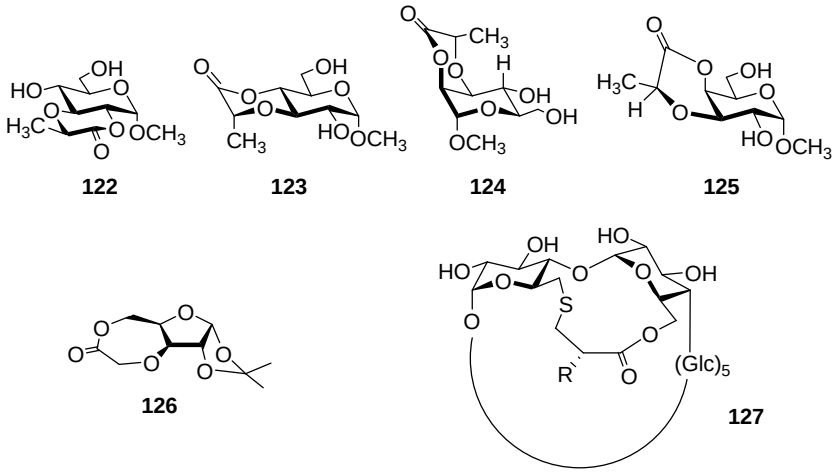


Scheme 33. Sialic acid lactones and derivatives.

4.2. Lactonized Carboxyalkyl Ethers and Glycosides

4.2.1. Non-Anomeric Carboxyalkyl Ethers

Various carboxyalkyl ethers at non-anomeric positions have been shown to give bicyclic systems which link positions 2,3 or 3,4 of sugars with various configurations through lactone formation. Examples are **122** and **123** (*gluco*), **124** (*manno)* and **125** (*galacto*), which were derived from 3-*O*-(1-carboxyethyl) substituted methyl glycosides [168, 169] (Scheme 34). Another example is the bicyclic caprolactone **126**, derived from 1,2,5,6-di-*O*-isopropylidene-α-D-glucofuranose in six steps [170]. Modified cyclodextrins of type **127** that involve lactonization of a carboxymethyl ether residue have also been reported [171].

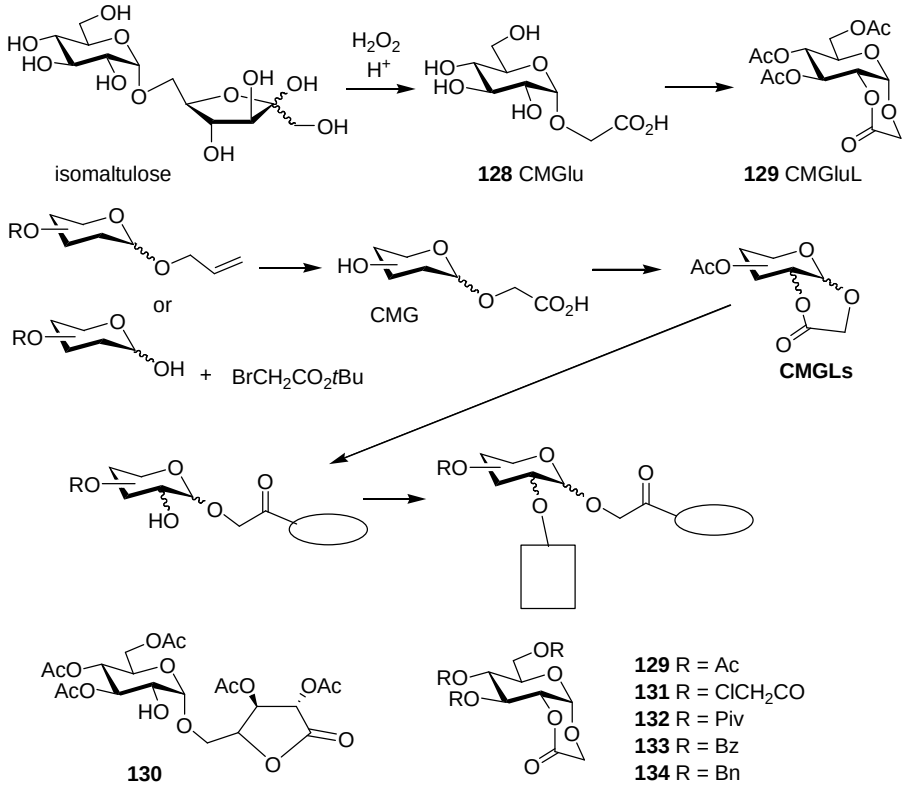


Scheme 34. Non-anomeric bicyclic lactones from carboxyalkyl ethers.

4.2.2. Anomeric Carboxymethyl Glycoside Lactones (CMGLs)

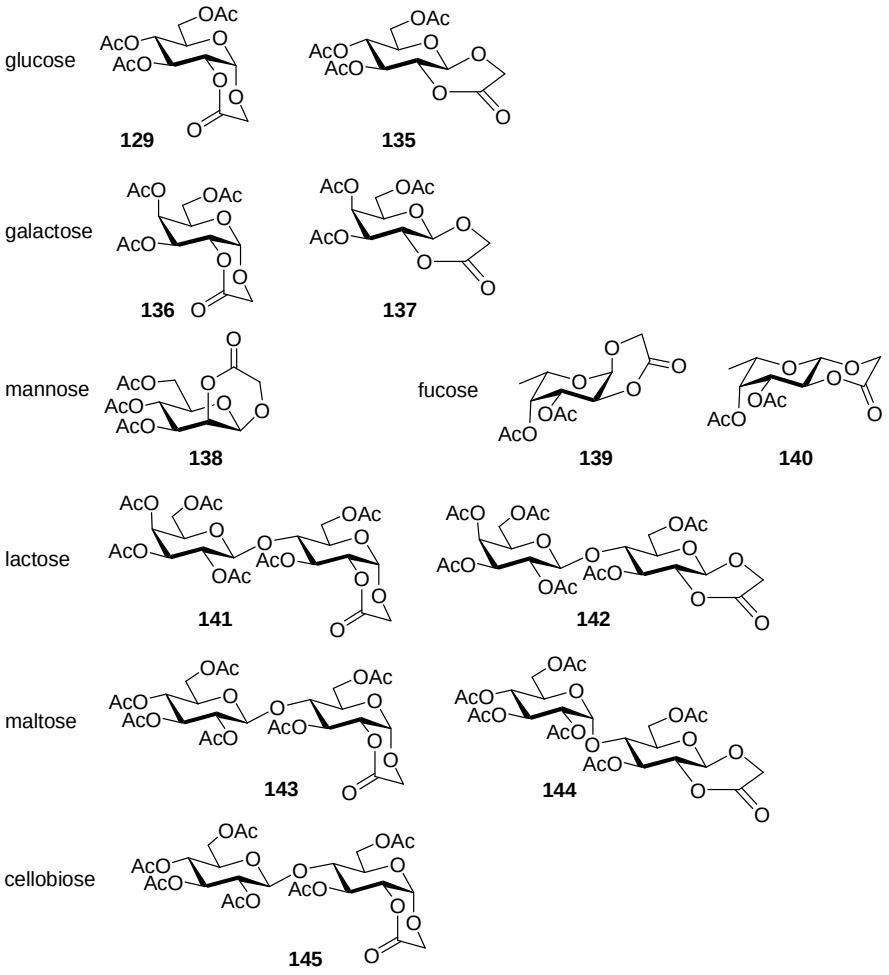
Queneau and co-workers have developed the chemistry of lactones involving the carboxymethyl residues linked to the anomeric hydroxy group and to OH-2 in several sugars [172–176]. Isomaltulose (Scheme 35) is obtained by bioconversion from sucrose and has been shown to be an interesting starting material for various applications [177–182]. Like isomaltulose, trehalulose, another glucose-fructose disaccharide, and the hydrogenated derivative of isomaltulose, Isomalt®, were all shown to lead to the same compound **128** (CMGGlu) by oxidation [183–185]. Acetylation of the latter compound led to bicyclic lactone **129**. Another lactone **130** was also observed as side product when the oxidative degradation of the fructose moiety of isomaltulose was incomplete [186]. The scope of the method was extended to bicyclic lactones other than the α-D-gluco one arising from isomaltulose. The oxidation of allyl glycosides and the anomeric alkylation of various sugars with *tert*-butyl bromoacetate allowed many structural variations, leading to a full toolbox of carbohydrate-containing synthons in both their anomeric forms, in most cases, including disaccharides [186, 187]. Moreover, the selective opening of the lactone ring of these compounds releases the free 2-OH position which is available for a second functionalization, leading to 1,2-bisfunctionalized carbohydrate derivatives. An explanation for these observations is that a mixed anhydride is formed by reaction of CMG with Ac_2O, followed by nucleophilic attack of OH-2. A similar structure, derived from β-lactoside, had been suggested [188] and a comparable system has been reported in a recent patent [189]. Not only were acetylated products prepared,

but also chloroacetyl, pivaloyl (Piv) or benzoyl (Bz) lactones **131–133**. The allyl glycoside route also permitted the preparation of lactones bearing another protecting group such as benzylated lactone **134** [186].



Scheme 35. Accesss to carboxymethyl glycoside lactones.

Non-protected aldoses or those peracetylated on all position except the anomeric hydroxy group react with *tert*-butyl bromoacetate (DMF, K_2CO_3) giving the corresponding *O*-glycosides [190, 191]. A significant selectivity for α anomers was observed for the reaction on the partially acetylated sugars, whereas some β selectivity (α:β from 1:1 to 1:2) was observed from free sugars. Galactose gives more complex mixtures in which the α-furanosides are the major products [192]. Lactones **129–145** have been prepared according to this route with subsequent treatment with Ac_2O in py (Scheme 36).

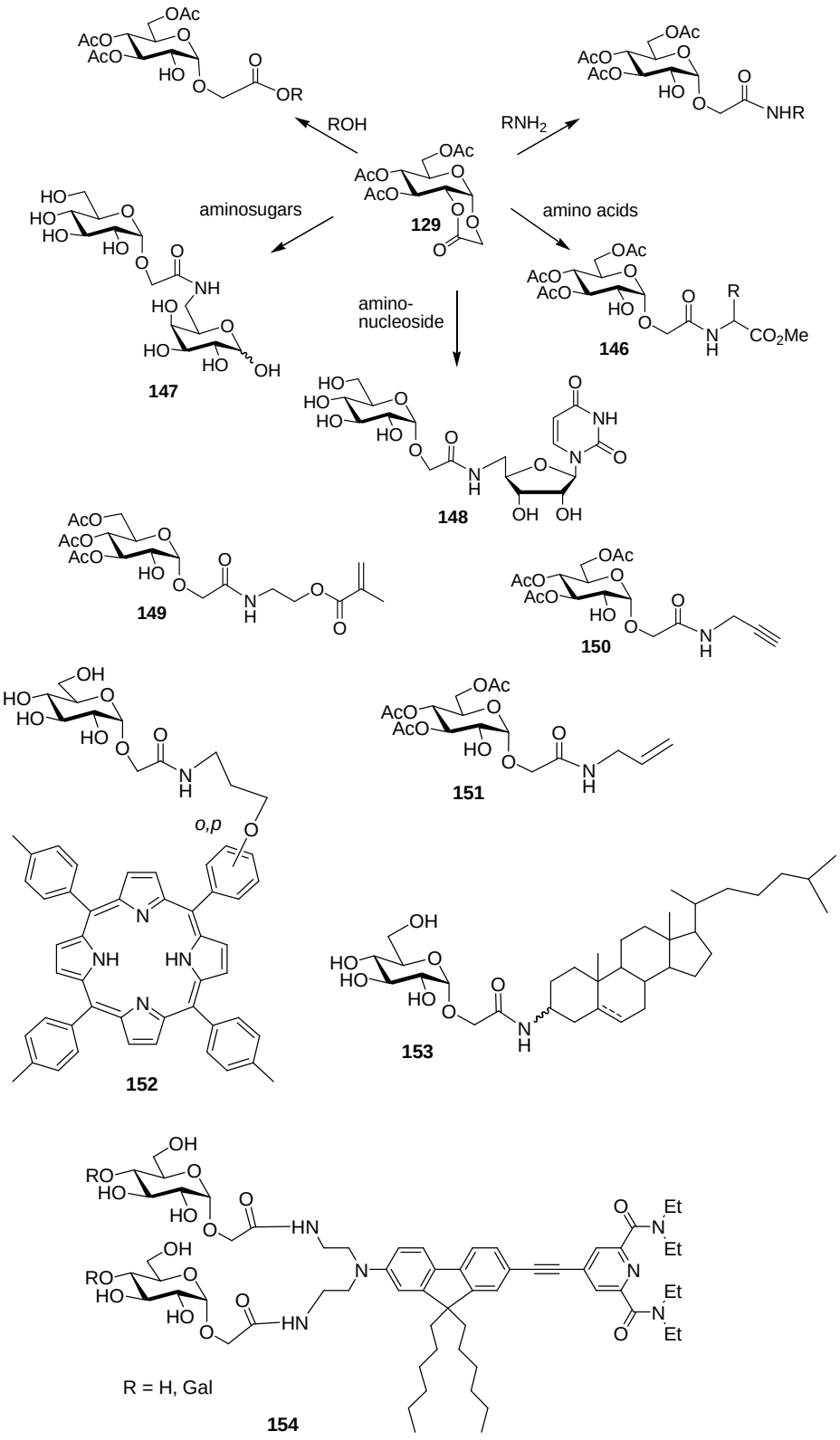


Scheme 36. Mono- and disaccharidic carboxymethyl glycoside lactones.

4.2.3. Use of CMGLs

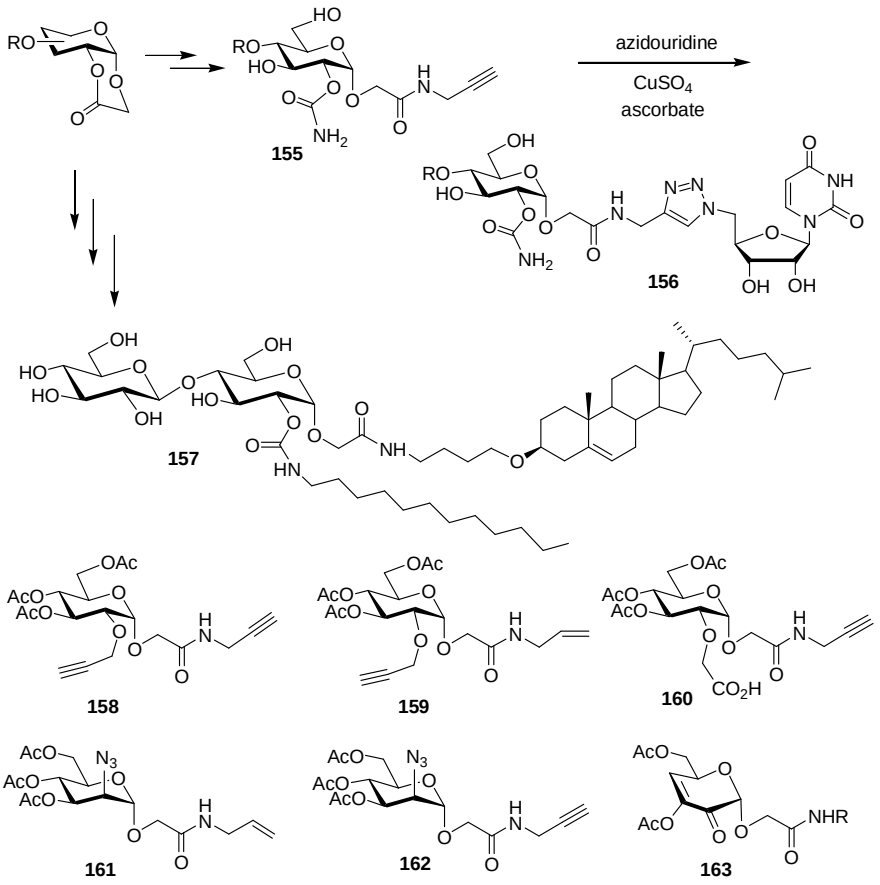
Alcohols react with carboxymethyl glycoside lactones (CMGLs) under either basic or acidic catalysis. However, the method is limited for acetylated targets, since deprotection of the acetyl groups cannot be achieved without substantial cleavage of the newly formed ester. Amines give stable amides (Scheme 37). Pseudo glycoamino acid hybrids of type **146** [184, 185], pseudo disaccharides **147**, and nucleotide sugars **148** [193] were thus obtained. With the idea that attaching a carbohydrate moiety can provide increased polarity and water solubility, other types of compounds were prepared by this method, such as polymerizable compounds of type **149–151**, and glycoporphyrins **152** designed as photosensitizers for cancer photochemotherapy [194, 195]. Pseudo glycolipids **153** were also prepared by this method [196], and more

recently new glycoprobes of type **154** for membranes nonlinear imaging have been derived from lactones **129** and **141** [197].



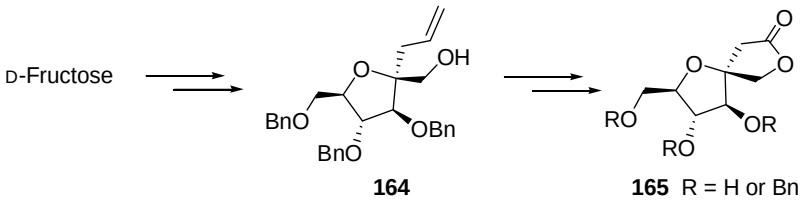
Scheme 37. Examples of conjugates obtained from carboxymethyl glycoside lactones.

Further functionalization at OH-2 was also explored [187]. From monosaccharidic (α-gluco, **129**) and disaccharidic (α-malto, **143**) CMGLs, several types of bisfunctionalized systems were synthesized by reaction with allylamine or propargylamine. For example, compound **155** was prepared and used in a synthesis of the nucleotide sugar analog **156** (Scheme 38). In the context of studies on the physicochemical behavior of synthetic glycolipids [198–204], new bisfunctionalized compounds such as **157** were recently obtained and found to possess very peculiar hysteretic thermotropic properties [205]. Reactions at OH-2 included carbamatations, etherifications leading to diynes, enynes and carboxy-ynes **158–160** [187]. Substitution by an azide after intermediate triflate formation led to azido alkenes or alkynes **161** and **162**, respectively. The reactivity of the latter compounds as AB monomers is presently being studied. Oxidation of OH-2 generates enones **163** [206].



Scheme 38. Bisfunctional compounds at C-1 and C-2 from CMGLs.

1-*C*-Allyl sugars have been transformed into spirobicyclic lactones which are the analogous synthons allowing the formation of *C*-glycosyl conjugates. For example, Araújo et al. prepared the intermediate **165** by C-allylation of the fully benzylated D-fructose followed by oxidation of the allyl group (Scheme 39) in the context of the evaluation of sugar-fused γ-butyrolactones and lactams as new potential γ-aminobutyric acid (GABA) receptor ligands [207].



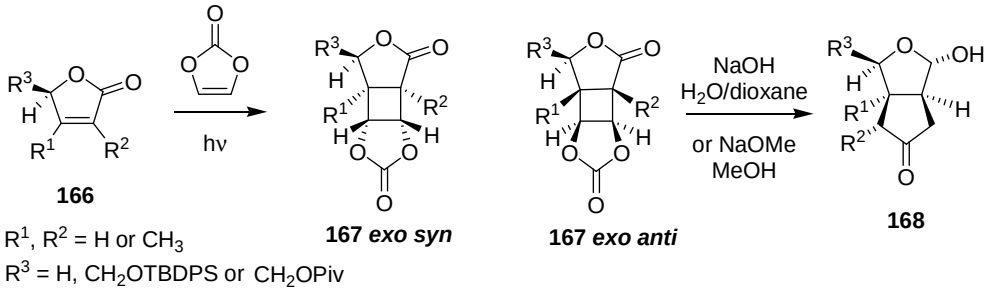
164 **165** R = H or Bn

Scheme 39. *C*-Glycosidic anomeric lactone from fructose.

4.3. Fused *C*-Branched Lactones

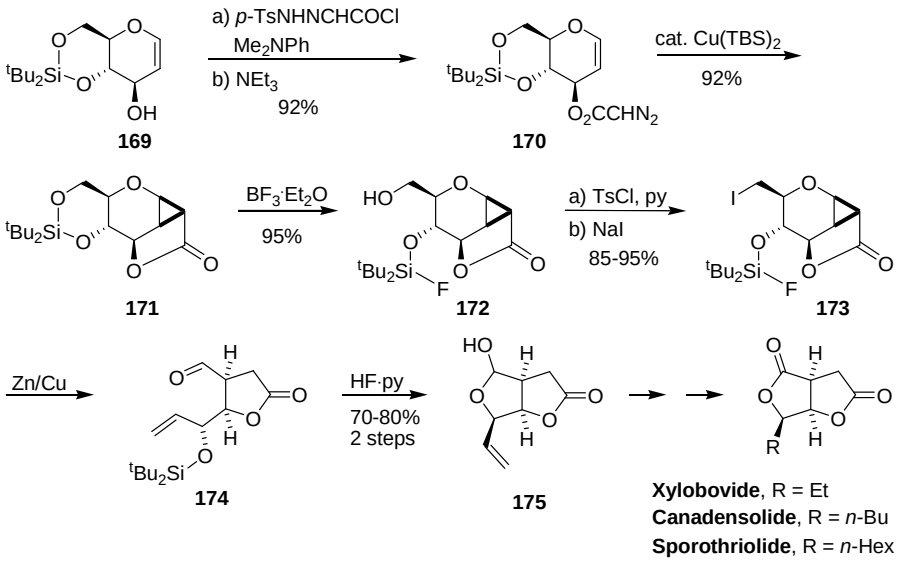
Five-membered lactones (γ-butyrolactones) fused to carbohydrates have proven to be convenient synthons towards branched-chain sugars through opening of the lactone unit.

Veláskes et al. [208] described the synthesis of γ-butyrolactones 2,3-fused to ribonucleosides by radical intramolecular addition in nucleosides comprising an α,β-unsaturated ester moiety at C-2 or at C-3 of the furanose ring. These bicyclic derivatives were further converted into 2-*C* or 3-*C*-branched chain nucleosides by opening of the lactone moiety with isobutylamine. Font and co-workers [209, 210] made use of homochiral butenolides as precursors for a stereoselective synthesis of γ-butyrolactones 2,3-fused to lyxofuranose units. Thus, photocycloaddition of vinylene carbonate to substituted butenolides (compounds type **166**, Scheme 40), gave selectively the corresponding *anti* cycloadducts **167** in moderate yields. The latter, when treated under basic conditions (0.5 M NaOH in water/dioxane or MeONa in MeOH), underwent rearrangement to afford the target bicyclic compounds **168** in modest to moderate yields.



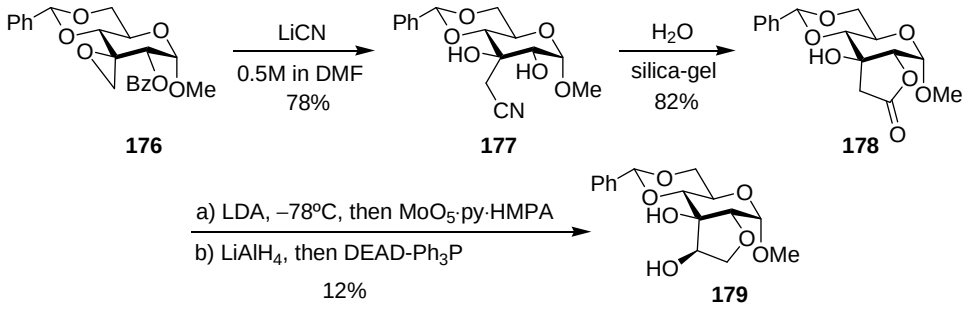
Scheme 40. Synthesis of furanose-fused γ-butyrolactones by photocycloaddition of vinylene carbonate to substituted butenolides.

The intramolecular cyclopropanation of 4,6-di-*O*-protected glycals (such as **169**) has been explored as a key step for the synthesis of advanced intermediates for bislactone natural products [211] (Scheme 41). The glycal-fused cyclopropane **171** was obtained by copper-catalyzed intramolecular cyclopropanation of the glycal-derived diazoacetate **170** in very good yield. It could then be converted into furanose-fused butyrolactone **175** in few steps, including selective monodeprotection to the alcohol **172** and further iodination. The resulting iodine derivative **173** was subjected to a zinc-mediated reductive ring opening cascade to furnish aldehyde **174**. Its desilylation provided bicyclic lactone **175** as a convenient precursor for xylobovide, canadensolide and sporothriolide bisfuranolactones.



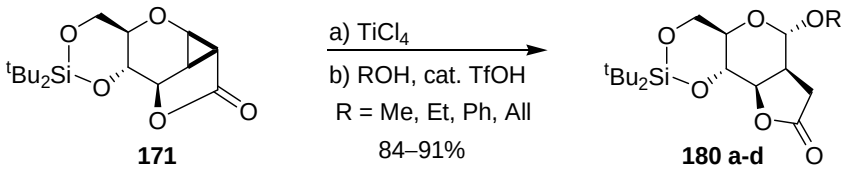
Scheme 41. Synthesis of a furanose-fused butyrolactone from a glycal-derived cyclopropane.

With respect to five-membered lactones fused to hexopyranose units, some approaches have been reported so far and the exploitation of their synthetic potential has led to the access of new carbohydrate derivatives. Bicyclic derivatives of this type are key intermediates in the synthesis of the epimer at C-3 of the sugar moiety contained in miharamycins [212, 213]. The latter are antibiotics known to inhibit strongly *Pyricularia oryzae*, which produces the rice blast disease and is considered a bioterrorism agent. Hence, the 3,3-spiroepoxide **176** was converted into the 3-*C*-cyanomethyl derivative **177**, the hydrolysis of which led to spontaneous cyclization in the presence of silica gel, giving the sugar-fused lactone **178** (Scheme 42). A stereoselective hydroxylation of the latter compound followed by reduction led to the desired miharamycin sugar moiety analogue **179**.



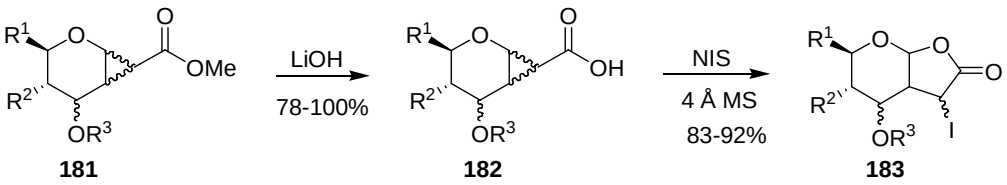
Scheme 42. Sugar moiety of miharamycins from hexopyranoside-fused butyrolactones.

The previously mentioned glycal cyclopropanation method was also applied to the synthesis of γ-butyrolactones 2,3-fused to glycopyranosides (Scheme 43) [214]. Hence, ring opening of the cyclopropane derivative **171** by $TiCl_4$, which was followed by in situ addition of alcohol, furnished glycoside-fused butyrolactones **180a–d**, in high yields and good diastereoselectivity (α/β ratio ranging from 6:1 to 15:1).



Scheme 43. Pyranoside 2,3-fused-γ-butyrolactones from a glycal derived cyclopropane.

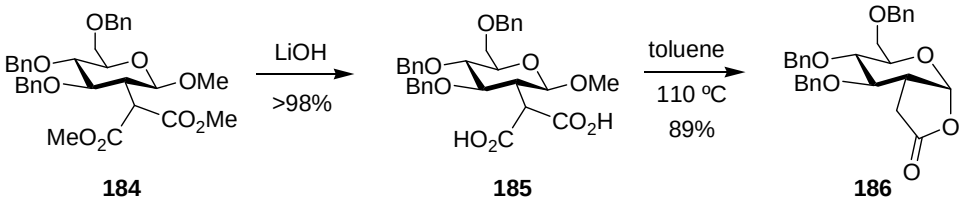
More recently, another methodology for sugar-fused butyrolactones employing glycal-derived cyclopropane precursors has been described by Chandrasekaran and co-workers (Scheme 44) [215]. In this case, hexofuranoid or hexopyranoid glycals were cyclopropanated into compounds of type **181**. After saponification with LiOH, giving **182**, iodination with *N*-iodosuccinimide (NIS) provided **183** resulting from homoiodolactonization.



181 **182** **183**

Scheme 44. Synthesis of sugar-1,2-fused iodobutyrolactones from sugar-1,2-fused cyclopropanated esters.

On their side, Yin and Linker [216] made use of a 2-*C*-branched hexopyranoside, the synthesis of which was achieved by addition of dimethyl malonate to tri-*O*-benzyl-D-glucal (IUPAC name: 3,4,6-tri-*O*-benzyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol, Scheme 45) [217]. Thus, saponification of the 2-*C*-[bis(methoxycarbonyl)]methyl derivative **184** to the corresponding malonic acid **185** was followed by heating in refluxing toluene. This led to decarboxylation and lactonization giving **186**. The method was optimized and applied to the synthesis of pentoses and disaccharides.

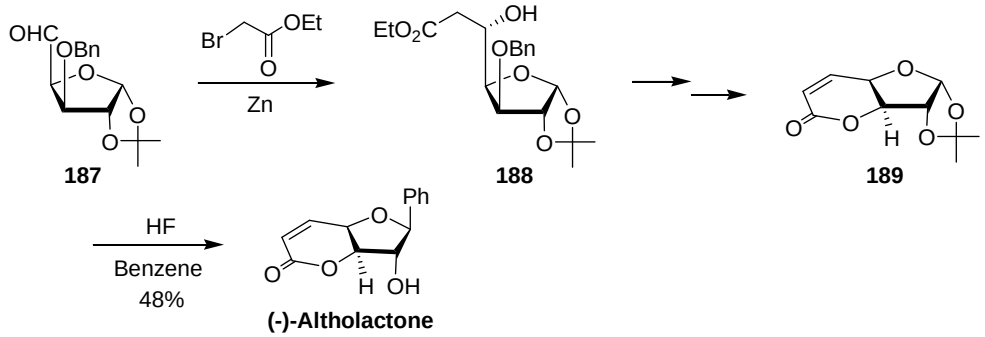


184 **185** **186**

Scheme 45. Synthesis of a hexopyranose-1,2-fused butyrolactone from a 2-*C*-malonyl glucoside.

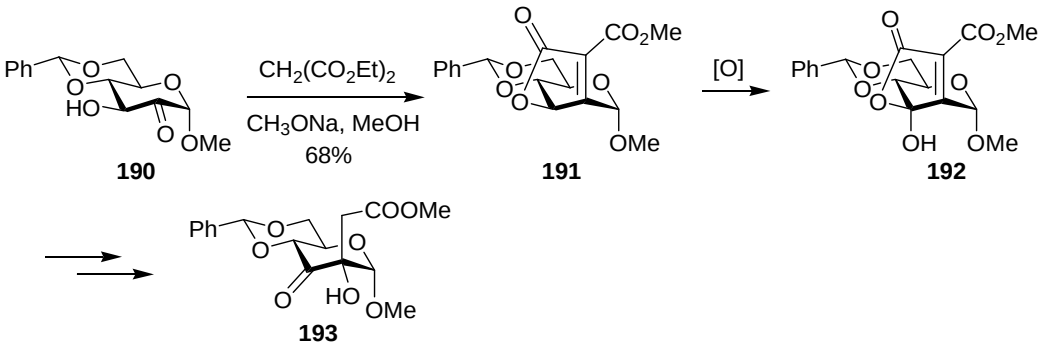
α,β-Unsaturated lactones are relevant motifs considering their ability to act as functionalized substrates for a variety of transformations. Some of them are bioactive [218–222]. An early synthesis of the enantiomer of (+)-altholactone (Scheme 46), a

natural product with cytotoxic and antitumor activities (for a review on the bioactivity of styryllactones see [223, 224]), involves the preparation of a furanose-fused α,β-unsaturated δ-lactone intermediate **189** [225]. Starting from a α-D-*xylo*-pentodialdofuranose derivative **187**, a Reformatsky reaction with ethyl bromoacetate introduces the carboxylic side chain necessary for intramolecular lactonization.



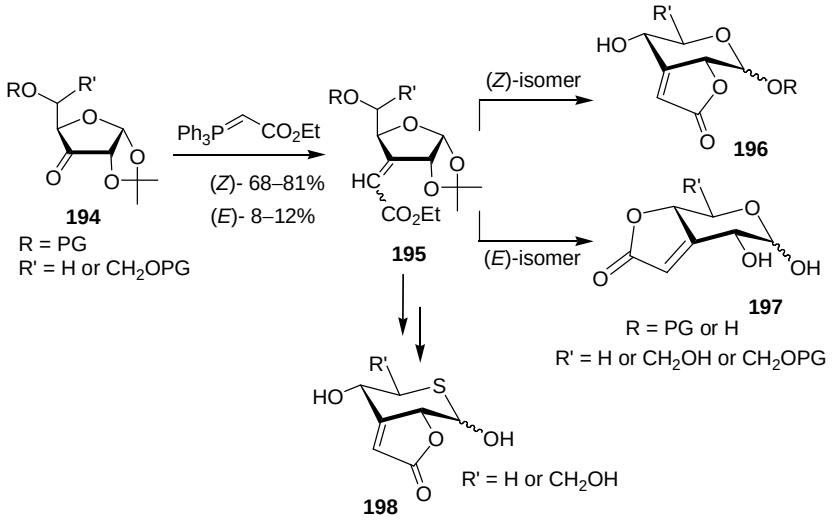
Scheme 46. Synthesis of the non-natural enantiomer of (+)-altholactone via a furanose-fused unsaturated δ-lactone.

A pentopyranoside-fused butenolide is the key intermediate for the synthesis of the natural micotoxin patulin [226, 227]. Its synthesis involves Wittig olefination of a 3,4-di-*O*-protected arabinopyran-2-uloside, followed by protecting group removal and dehydration (Scheme 47). In another research, the glucopyranosid-2-uloside **190** was converted into the butenolide derivative **191** by aldol condensation with diethyl malonate and transesterification [228]. The latter was shown to be prone to autoxidation, leading to **192**. Subsequent Michael addition with hydroxide ion, followed by decarboxylation, furnishes *C*-branched-chain sugar **193**.



Scheme 47. Synthesis of a 2-*C*-branched-chain sugar via a pyranose-fused butenolide.

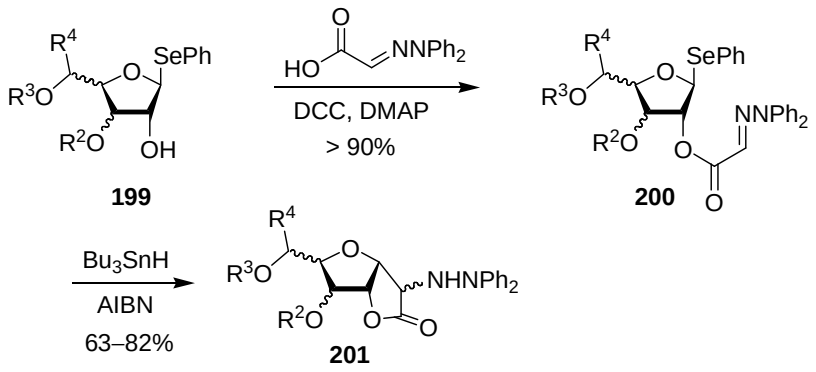
An elegant stereocontrolled route for pyranose-fused butenolides starting from easily synthesized protected furanos-3-uloses (compounds of type **194**) has been reported [229, 230] (Scheme 48). It consisted of the synthesis of 3-*C*-branched α,β-unsaturated esters (**195**) by Wittig olefination, followed by acid hydrolysis. Within this latter step, cleavage of the protecting groups (PG), intramolecular transesterification, and furanose-pyranose isomerization occurred, furnishing directly the target bicyclic compounds (**196**, **197**) in good overall yields. This approach was convenient for achieving in few steps both pento- and hexopyranose-based bicyclic systems comprising the butenolide moiety anchored at C2-C3 or at C3-C4 of the sugar ring, depending on the configuration around the C3-C3' double bond. The feasibility and scope of this methodology were then investigated for the preparation of 5-thiopento or hexopyranose analogues of type **198** [231]. Thus, after introduction of an additional sulphydryl functionality at C-5 at the intermediate α,β-unsaturated esters, acid hydrolysis also allowed ring expansion to the thiopyranose form with accompanying butenolide formation, generating new highly functionalized and potential biologically interesting bicyclic thiosugar-based systems.



Scheme 48. Synthesis of butenolides fused to pento- or hexopyranoses and thiosugar analogues from furanos-3-uloses.

Fused *C*-glycosyl lactones are also suitable synthons for further elaboration into more complex *C*-glycosyl compounds, including glycoconjugates. In one of the few published methods to afford these bicyclic lactones, protected 1-phenylseleno glycosyl donors possessing a free OH-2 (compounds of type **199**) were converted into the

corresponding 2-hydrazonoesters **200**. The latter were then subjected to radical cyclization (Scheme 49) [232] giving α-hydrazino lactones **201** that could be transformed into the corresponding *C*-glycosyl amino acids through standard functional manipulations.



Scheme 49. Synthesis of furanose-fused *C*-glycosyl α-hydrazino lactones from phenyl-1-seleno glycosyl donors.

5. Conclusion

Lactones derived from carbohydrates are building blocks of high synthetic potential. Next to the readily available aldonolactones and uronic acid lactones, some bicyclic systems have recently emerged as useful synthons. Examples of applications encompass functional derivatives such as polymers, as well as more elaborated compounds of physico-chemical or biological relevance.

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1.2. Sugars Containing α,β-Unsaturated Carbonyl Systems

The following subchapter was published as:

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It covers the synthetic approaches developed for this type of compounds as well their relevance as scaffolds for a variety of important sugar derivatives. Their potential as bioactive substances is also highlighted.

Carbohydr. Res. **2008**, *343*, 1523−1539

Sugars Containing α,β-Unsaturated Carbonyl Systems: Synthesis and Their Usefulness as Scaffolds in Carbohydrate Chemistry

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Keywords: α,β-Unsaturated carbonyl systems / Sugar-fused unsaturated lactones / Sugar-linked unsaturated lactones / Sugar-linked unsaturated ketones / α,β-Unsaturated pyranuloses.

Abstract

The α,β-unsaturated carbonyl function occurs in a wide variety of bioactive natural products. It is usually associated with the bioactivities of these compounds and acts as Michael acceptors for the addition of protein nucleophilic groups**.** The design and synthesis of sugars containing this functionality has provided a wide range of compounds, which can serve as building blocks of high synthetic versatility. This review deals with the chemistry of sugar-based molecules bearing singly linked or fused unsaturated lactones and ketones along with that of pyranoid enones and enonolactones. Examples are given of their syntheses and transformations into a variety of complex sugar derivatives such as branched-chain sugars, *C*-nucleosides, *C*-glycosyl derivatives, and various natural products, including selected analogues.

Contents

1. Introduction

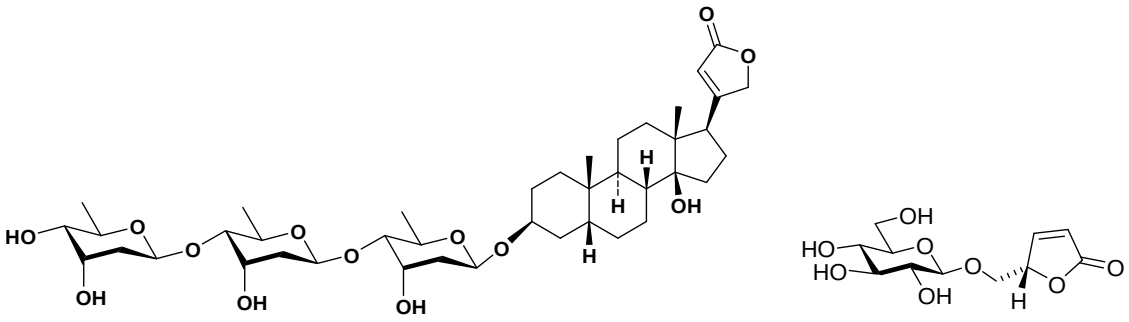
The α,β-unsaturated carbonyl moiety is present in a large number of natural and synthetic products exhibiting a variety of biological properties. Compounds containing such an unsaturated system, notably lactones or cyclic ketones, were described as cytotoxic [1a-e] and anti-tumor agents [1b], antimicrobials [1f] or as possessing significant antiviral [1b], gastric anti-ulcer activities [1g], among others. Furthermore, it has been shown that the conjugated system plays a fundamental role in determining bioactivity, due to its ability to act as a Michael acceptor for the addition of protein functional groups [2]. In particular, sugars incorporating unsaturated carbonyl motifs have become important synthetic targets not only due to their potential biological profile but also for their use as precursors for the synthesis of many bioactive compounds such as branched-chain sugars or nucleosides.

This review attempts to cover the synthetic strategies used to obtain sugar derivatives containing unsaturated carbonyl moieties in their structure, namely α,β-unsaturated lactones and cyclic ketones. It focuses on the natural occurrence and biological

relevance of these compounds, as well as on their use as important intermediates in carbohydrate chemistry.

2. Sugar Derivatives Containing α,β-Unsaturated Lactones

The ring system of α,β-unsaturated lactones, specially γ- and δ- lactones, constitutes the central skeleton of many natural products and is commonly related to a wide range of pharmacological activities. This biological behavior has prompted the investigation of synthetic methodologies for the generation of such motifs over the years [3]. Examples of naturally occurring glycosides containing α,β-unsaturated lactones include the cardiotonic digitoxin [4], which possesses a butenolide ring at position C17β in the steroid framework, and the butenolide glycoside ranunculin (Fig. 1) [5].



Digitoxin **Ranunculin**

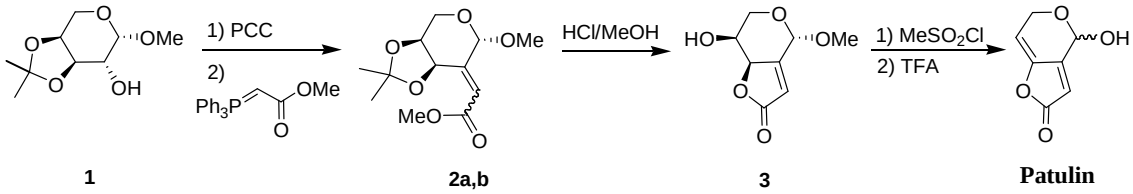
Figure 1. Two examples of naturally occurring glycosides containing α,β-unsaturated lactones.

We discuss below the methods that have been employed for the preparation of sugar-linked, sugar-fused or sugar-based unsaturated lactones, focusing on five- and six-membered ring systems.

2.1. γ-Lactones

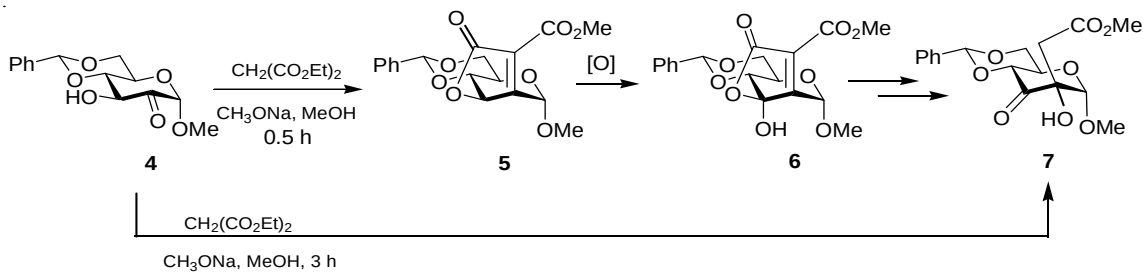
2.1.1. γ-Lactones Fused to Sugars

Five-membered ring unsaturated lactones fused to carbohydrates, namely butenolides [2(5*H*)-furanones], have been used as intermediates for the synthesis of bioactive natural products and branched-chain sugars. This moiety is a structural unit of the mycotoxin patulin (Scheme 1), produced by different species of *Penicillium*, *Aspergillus*, and *Byssochlamys*, which shows significant antibiotic and antibacterial properties, despite being a food contaminant and a general plant toxin [6]. Its synthesis involved oxidation of methyl 3,4-*O*-isopropylidene-β-L-arabinopyranoside **1**, easily prepared from L-arabinose, followed by Wittig olefination of the resulting keto sugar to afford an approximately 3:l mixture of the (*E)*- and (*Z)*-unsaturated esters **2a,b**. The (*E)*-isomer was subsequently converted into the sugar-fused butenolide **3** after hydrolysis with dilute hydrochloric acid in methanol under reflux. Dehydration of **3** by mesylation–elimination provided (*S*)-*O*-methylpatulin, which was then deprotected by treatment with trifluoroacetic acid (TFA) to produce the target molecule.



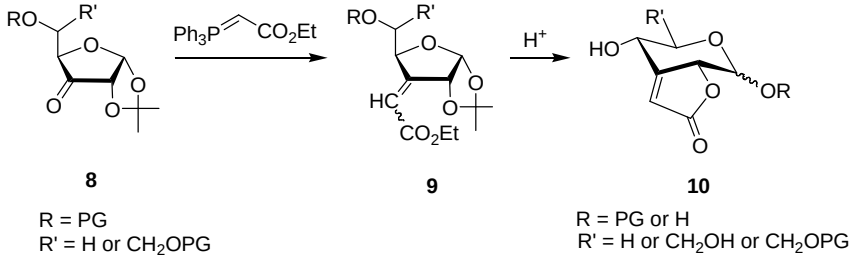
Scheme 1. Synthesis of patulin.

Liu et al. [7] reported the autoxidation of a hexopyranoside-fused butenolide **5,** which was isolated as an intermediate in the one-pot synthesis of the 2-*C*-branched-chain sugar **7**. Insights into the mechanism of this transformation clarified the three main steps involved. Thus, aldol condensation of the glucopyranosid-2-ulose **4** with diethyl malonate proceeded via the butenolide **5**, which was obtained by transesterification and intramolecular cyclization **(**Scheme 2**)**. This compound was then transformed into **6** by autoxidation. The latter underwent Michael addition in the presence of water, which was followed by decarboxylation, leading to the corresponding branched-chain sugar **7**.



Scheme 2**.** Steps involved in the synthesis of the 2-*C*-branched-chain sugar **7**.

We have also demonstrated an efficient preparative access to butenolides fused to pento- and hexopyranoses (compounds-type **10**) in a few steps starting from commercially available furanose derivatives (Scheme 3) [8a]. The methodology consists on the Wittig olefination of furanos-3-uloses (compounds of the general type **8**), which are easily obtained, followed by acid hydrolysis. This step leads to the cleavage of the acid labile protecting groups (PG), intramolecular lactonization and isomerization to the pyranose form. Using this synthetic pathway, good overall yields were obtained for the target compounds.

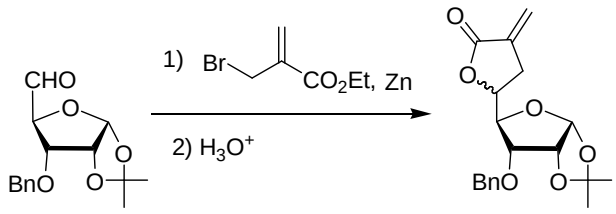


Scheme 3. Synthesis of butenolides fused to pento- and hexopyranoses using furanos-3-uloses as precursors.

Synthesis of this type of sugar-fused butenolides, using a similar strategy, was published soon afterwards by Goddard-Borger et al. [8b]. These molecules were subsequently transformed into 3-methyl-2*H*-furo[2,3-c]pyran-2-ones by elimination with DBU.

2.1.2. γ-Lactones Linked to Sugars

Sugar linked α,β-unsaturated γ-lactones, notably butenolides and α-methylene-γ-butyrolactones, have attracted much attention owing to their biological and pharmacological properties and their role as synthons for useful sugar derivatives. Our research group has contributed to this field using two different approaches. The introduction of an α-methylene-γ-butyrolactone on a furanose residue (**12a**,**b**) was achieved by a Reformatsky-type reaction of a dialdofuranose **11** with ethyl bromomethylacrylate and zinc to give both C-5 epimers which were easily separated by liquid chromatography (Scheme 4) [9]. Some of these compounds proved to have significant fungicidal activity and were particularly effective against *Puccinia recondita*, *Botrytis cinerea* and *Plasmopara viticola*, being considered to be wheat-, pepper- or wine-protective agents, respectively [9b].

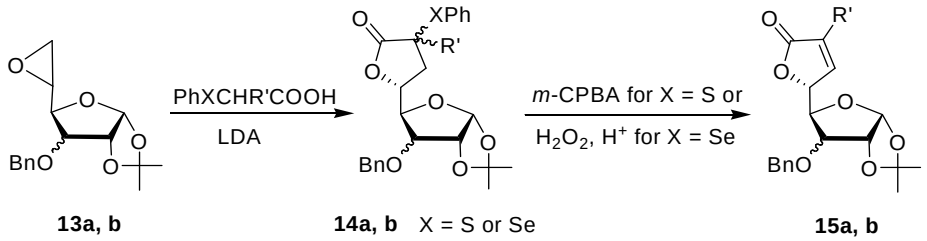


11 **12a, b**

Scheme 4. Synthesis of antifungal sugar-linked α-methylene-γ-lactones.

The other approach led to the synthesis of a sugar containing an endocyclic unsaturated lactone functionality, starting from sugar epoxides having the *gluco*- or *allo*-configuration (**13a**,**b**, Scheme 5). Reaction with the dianion of phenylselenoacetic or -propionic acids, or their thioanalogues, followed by oxidation and elimination afforded the target molecules (**15a**,**b**). The configuration of the single diastereoisomer formed is determined by that of the epoxide starting material [9b,c]. Biological testing of these compounds has demonstrated their efficacy as insecticides for a number of arthropode species such as *Musca domestica* L. (housefly), *Trialeurodes vaporariorum* (Westwood) (glasshouse whitefly), *Drosophila melanogaster* Meig (fruitfly), being particularly potent and selective against fruitflies, and much more active than imidacloprid, the insecticide commercially used. In addition, the compounds were not

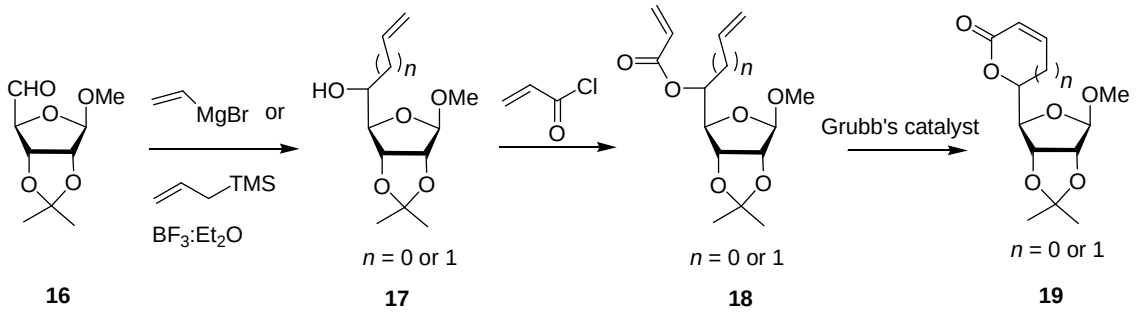
toxic to *Artemia salina* L. (brine shrimps), a reference organism for the evaluation of the potential toxicity hazard to invertebrates in ecosystems [10].



13a, b **14a, b** X = S or Se **15a, b**

Scheme 5. Synthesis of sugar-linked butenolides from epoxide precursors.

The ring-closing metathesis (RCM) of acrylates derived from allylic and homoallylic alcohols has been a convenient reaction to form five-and six-membered unsaturated lactones [3b]. The method has been successfully employed in sugar scaffolds to give C-linked γ- and δ-unsaturated lactones (Scheme 6). The methodology published by Gosh *et al*. [11] started from the pentodialdose **16**, which was treated with vinylmagnesium bromide or allyltrimethylsilane to give the homoallylic alcohol **17**, which when acylated with acryloyl chloride afforded the acrylate esters **18.** These compounds were subjected to RCM in the presence of Grubbs' catalyst to furnish α,β-unsaturated γ- or δ-lactones **19**. A similar procedure was used for the formation of unsaturated macrocyclic (nine- to fifteen-membered) lactones linked to sugars [12].

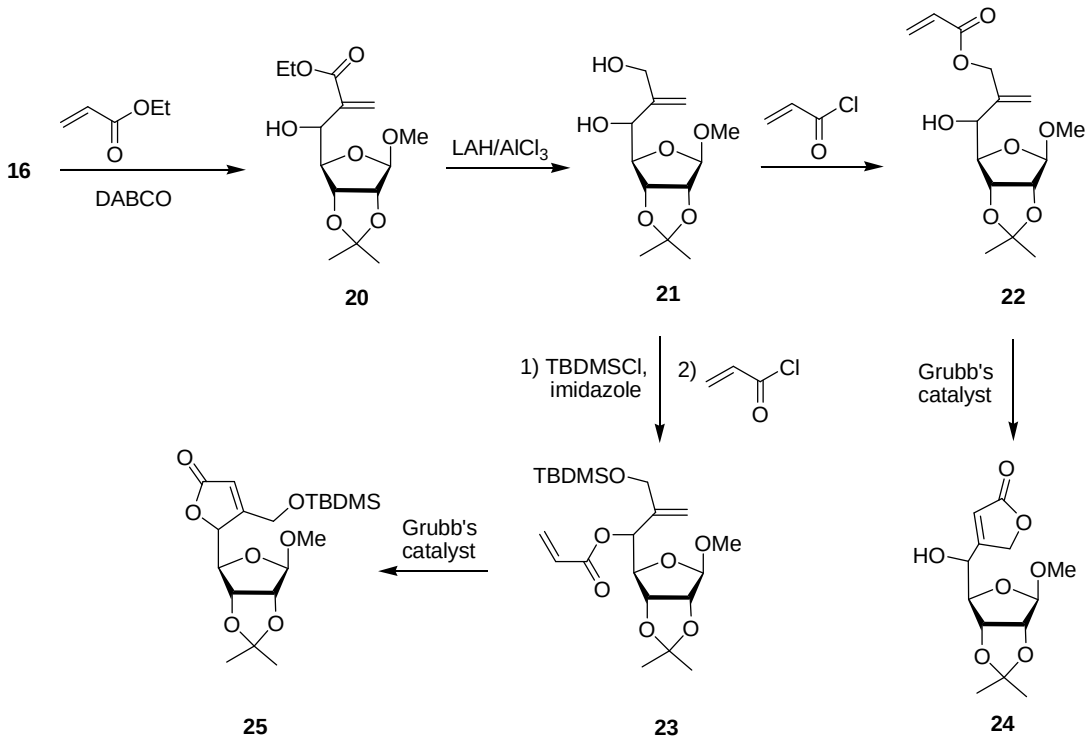


16 **17** **18** **19**

Scheme 6. Synthesis of sugar-linked γ and δ-unsaturated lactones by RCM starting from dialdofuranoses**.**

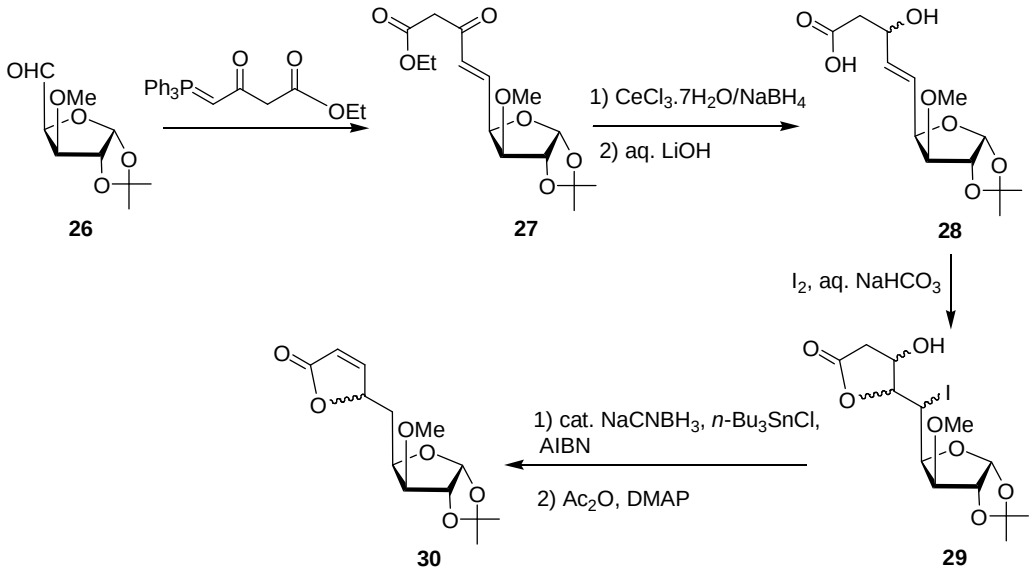
An alternative route to sugar-linked butenolides was based on the conversion of the precursor dialdofuranose (**16**) into Baylis-Hillman adducts (Scheme 7) [13]. Reduction

of the resulting alkene **20** to the corresponding diol **21**, followed by monoacryloylation at the primary or at the secondary hydroxyl group, gave the corresponding acrylate esters **22**–**23**. The latter compounds, upon RCM, led to the sugar-linked 4-substituted-γ-lactone **24** or the 4,5-disubstituted-γ-lactone **25**.



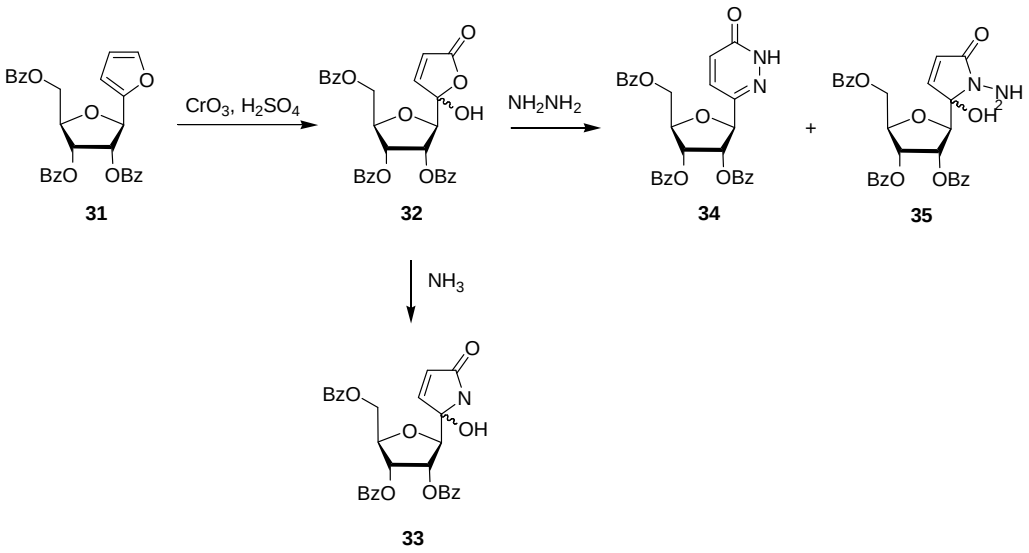
Scheme 7. Synthesis of sugar-linked butenolides by combination of Baylis-Hillman reaction with RCM**.**

Another useful synthetic tool involved Wittig and iodolactonization reactions using dialdofuranoses as the starting materials (Scheme 8), aiming at sugar-linked butenolides, which were then converted into the corresponding isoxazolidine derivatives [14]. Thus, Wittig olefination of **26** with ethyl 3-oxo(triphenylphosphorylidene)-butanoate gave the alkene **27** as an inseparable keto–enol mixture, which on reduction, followed by hydrolysis resulted in the formation of **28**. This compound was converted into the lactone **29** by reaction with I_2 in the presence of aq. $NaHCO_3$. Subsequent deiodination of **29** with catalytic $NaCNBH_3$–tributyltin chloride, followed by acetylation, provided the butenolide **30.**



Scheme 8. Synthesis of sugar-linked butenolides by the Wittig olefination-iodolactonization approach.

Maeba et al. [15] also made use of the versatility of the butenolide moiety to be converted in heterocyclic systems for the synthesis of *C*-nucleosides. The α,β-unsaturated lactone **32**, C-linked to the anomeric position, was prepared by Jones oxidation of the β-D-ribofuranosyl derivative **31 (**Scheme 9**)**. The key intermediate **32** was further transformed into *C*-nucleosides **33**–**35** possessing pyrrolinone, pyridazinone, and *N*-aminopyrrolinone rings in their structure.

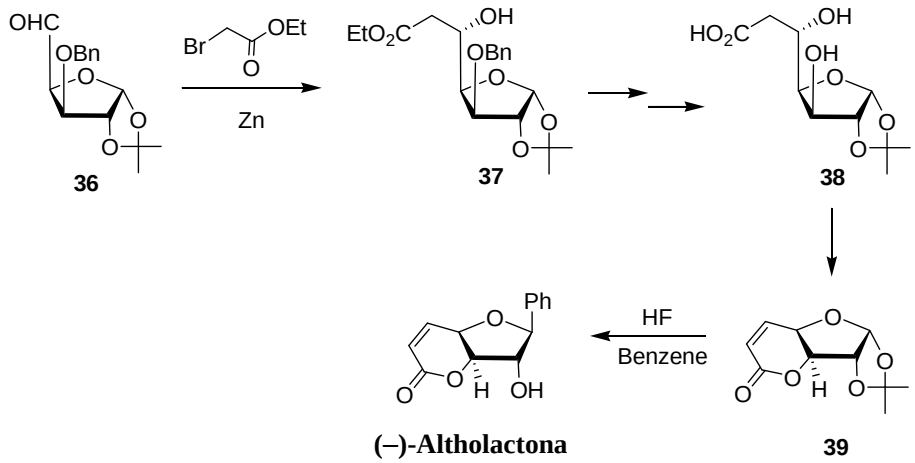


Scheme 9. Synthesis of a *C*-glycosyl butenolide and its conversion into *C*-nucleosides.

2.2. δ-Lactones

2.2.1. δ-Lactones Fused to Sugars

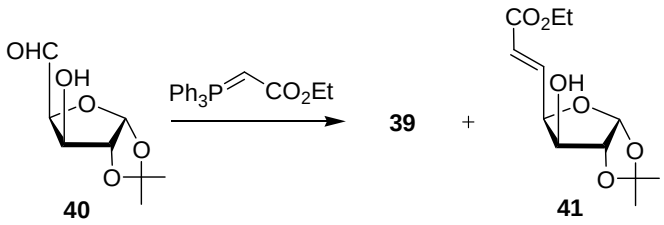
Sugar-derived unsaturated δ-lactones have been used as precursors in the synthesis of some naturally occurring compounds, because of their natural product-like profiles, and the possibility of taking advantage of the chirality resident in the sugar moiety. For example, a furanose-fused α,β-unsaturated δ-lactone was a key intermediate for the preparation of the enantiomer of (+)-altholactone, as reported by Gesson et al. [16] (Scheme 10). This sugar-derived bicyclic lactone was isolated from an unknown *Polyalthea* species and from various *Goniothalamus* species and is known to be cytotoxic in vitro showing considerable antitumor activity in vivo [17]. The procedure consisted of a Reformatsky reaction of the aldehyde **36** with ethyl bromoacetate. The resulting β-hydroxy ester **37** was converted into a dihydroxy acid **38** after ester hydrolysis and debenzylation. This latter compound was dehydrated to the furanose-fused unsaturated δ-lactone **39.** Treatment of **39** with hydrogen fluoride in benzene furnished (–)-altholactone.



Scheme 10. Synthesis of the non-natural enantiomer of (+)-altholactone via a furanose fused unsaturated δ-lactone.

An alternative procedure for the synthesis of the unsaturated-δ-lactone **39** was based on a Wittig reaction of 1,2-*O*-isopropylidene-α-D-*xylo*-pentodialdofuranose **40** with [(ethoxycarbonyl)methylene]triphenylphosphorane, followed by intramolecular

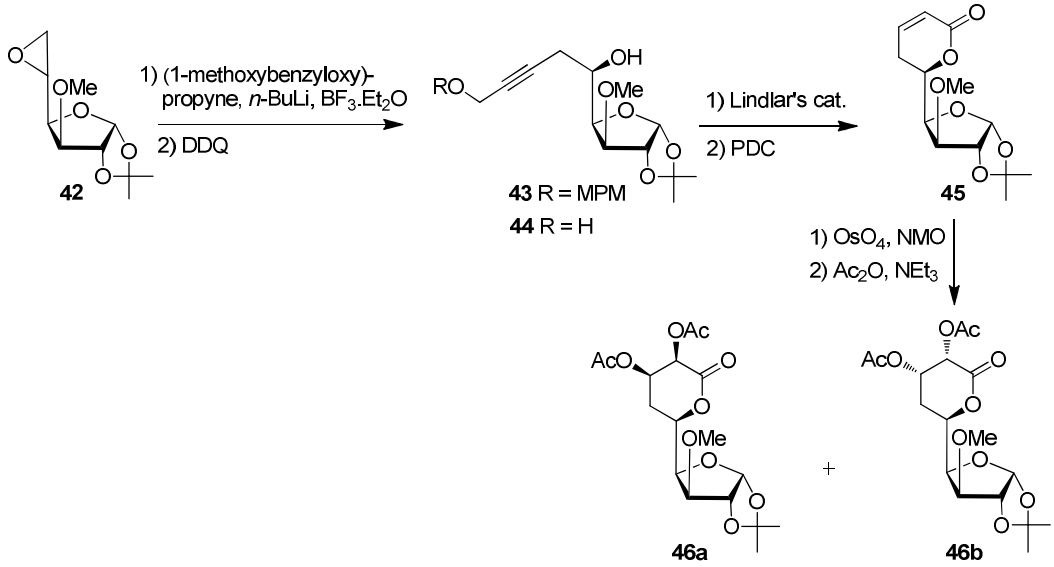
lactonization of the (*Z*)-α,β-unsaturated ester (Scheme 11) [18].



Scheme 11. Synthesis of the furanose-fused unsaturated δ-lactone **39** by the Wittig olefination–intramolecular cyclization approach.

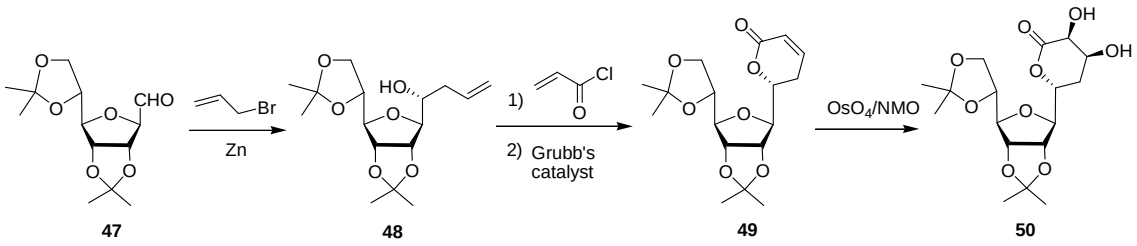
2.2.2. δ-Lactones Linked to Sugars

We have previously cited the synthesis of α,β-unsaturated δ-lactones linked to sugars by RCM (see Scheme 6). Another approach to these compounds consists of reaction of the epoxide **42** with (1-methoxybenzyloxy)propyne in the presence of *n*-BuLi to afford the alkyne **43**, which, after deprotection of the primary position, gave diol **44** (Scheme 12). Subsequent alkyne reduction with Lindlar's reagent followed by oxidation furnished the α,β-unsaturated δ-lactone **45**, which was successfully used to prepare the C–C-linked disaccharides **46a** and **46b** by *cis*-dihydroxylation/acetylation [19].



Scheme 12. Synthesis of furanose-linked α,β-unsaturated δ-lactone and its conversion into C(4)–C(5)-linked disaccharides.

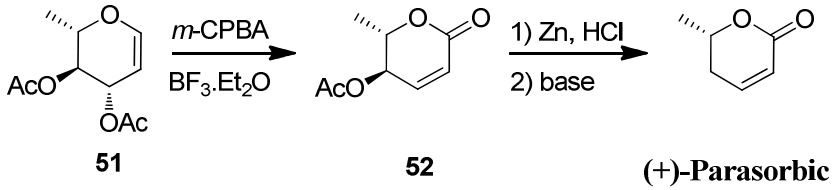
The RCM protocol also proved useful in providing a short route to disaccharides (Scheme 13) [20]. Accordingly, the reaction of the aldehyde **47** with allyl bromide and activated zinc gave the alcohol **48**, which acroylation, followed by RCM, led to the unsaturated δ-lactone **49**. The target molecule **50** was obtained by *cis*-dihydroxylation of **49** upon treatment with osmium tetroxide.



Scheme 13. Synthesis of C(1)–C(5)-linked disaccharides from furanose-linked α,β-unsaturated δ-lactones.

2.2.3. Pyranoid δ-Lactones

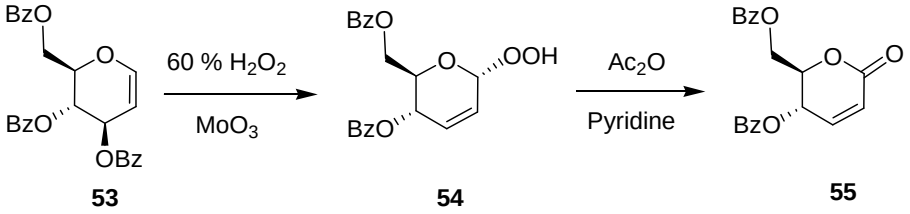
Sugar-derived pyranoid α,β-unsaturated δ-lactones (5,6-dihydropyran-2-ones) are easily synthesized from glycals, and have been widely used as key chiral intermediates for the preparation of biologically active natural products [3a, 21]. In 1982, Jarglis and Lichtenthaler described a one-step procedure for 2,3-unsaturated lactones by oxidation of glycals and 2-acyloxyglycal esters with *m*-chloroperbenzoic acid (*m*-CPBA) or pyridinium chlorochromate (PCC) in the presence of boron trifluoride etherate [22]. This straightforward transformation was a key-step for the synthesis of (+)-parasorbic acid (Scheme 14) [23].



Scheme 14. Synthesis of (+)-parasorbic acid via enonolactone **52,** which was obtained by $BF_3.Et_2O$-induced peroxidation of the L-rhamnose-derived glycal **51.**

The BF_3-mediated peroxidation of a glycal proceeds via a generation of an allylcarboxonium ion, which undergoes subsequent peroxidation to give an intermediate 1-peroxyacyl-hex-2-enopyranose, which upon fragmentation affords the pyranoid enonolactone [22, 24].

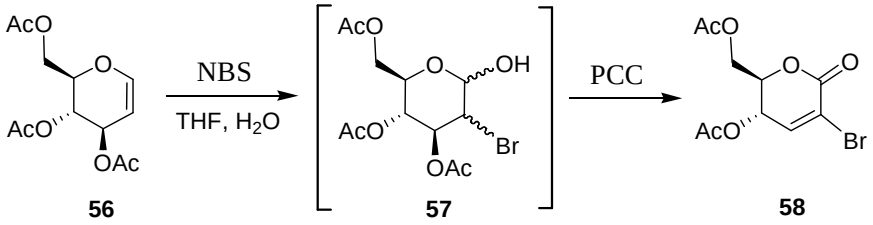
The oxidation of glycals involving anomeric hydroperoxides as intermediates has been carried out using other catalysts. Fehlhaber et al. reported the oxidation of 1,5-anhydro-3,4,6-tri-*O*-acetyl-2-deoxy-D-*arabino*-hex-1-enitol (non-preferred trivial name: 3,4,6-tri-*O*-acetyl-D-glucal) to the corresponding hydroperoxide with 85% hydrogen peroxide in dioxane, in the presence of sulphuric acid [25]. A different approach, starting from the correponding benzoyl protected glycal (**53**), also employed hydrogen peroxide as oxidizing agent and made use of molybdenium trioxide as catalyst. The obtained hydroperoxide (**54**) could be converted into unsaturated lactone **55** via dehydration on treatment with Ac_2O/py (Scheme 15) [26a,b]. In addition, 2-*C*-methylene-hydroperoxides could also be converted into the corresponding exocyclic α,β-unsaturated δ-lactones [26b,c].



53 **54** **55**

Scheme 15. Synthesis of the pyranoid 2-enono-1,5-lactone **55** by oxidation of tri-*O*-benzoyl-D-glycal **53** to the hydroperoxide **54,** followed by dehydration.

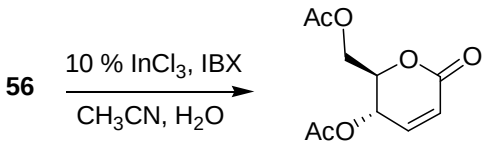
PCC oxidation has also been commonly used for the direct synthesis of sugar-derived pyranoid α,β-unsaturated δ-lactones from glycals [27]. A different methodology for the conversion of glycals to enonolactones has been reported by Rauter et al. [28]. Thus, reaction of the glycal **56** with NBS and water, followed by oxidation of the intermediate 2-bromolactol **57** with PCC, afforded the 2-bromo-enonolactone **58**. Further biological assays demonstrated the high insecticidal activity of this compound against fruitflies [10].



56 **57** **58**

Scheme 16. Synthesis of the insecticidal pyranoid 2-bromo-enonolactone **58.**

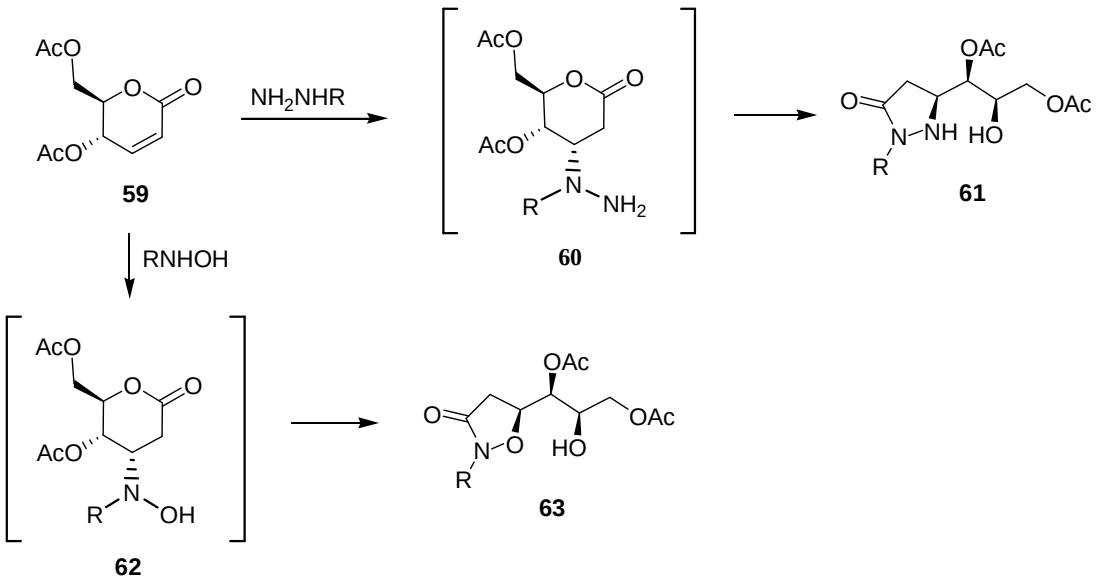
The mild oxidizing agent iodoxybenzoic acid (IBX), in combination with indium trichloride, proved to be an efficient system for the one-pot conversion of glycals to enonolactones (Scheme 17) [29]. The reaction involves most likely an indium mediated allylic rearrangement, followed by oxidation of the corresponding lactol.



59

Scheme 17. Synthesis of enonolactone **59** by $InCl_3$–mediated oxidation of the glycal **56** with IBX.

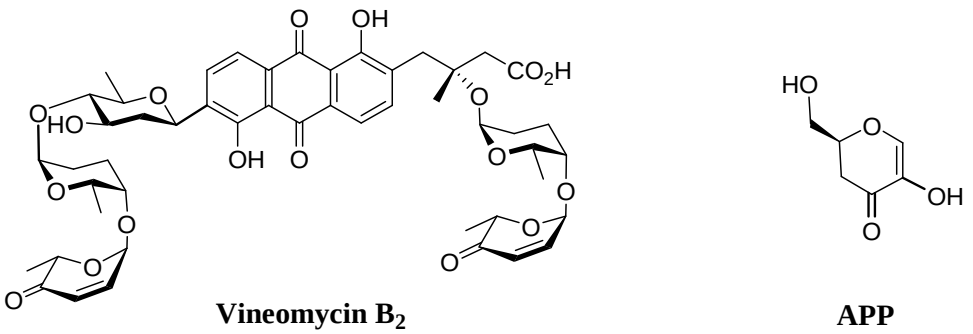
The versatility of these sugar derivatives as synthons has encouraged their use as precursors for the preparation of bioactive compounds and natural products, typically as Michael acceptors or dipolarophiles in cycloaddition reactions [30]. In particular, the conjugate addition of hydroxylamines and hydrazines to sugar enonolactones has been a suitable method to access various optically active heterocycles such as pyrazolidin-3-ones and isoxazolidin-5-ones, which are useful intermediates for the synthesis of β-lactam antibiotics. Chmielevski and co-workers [30a,b] described the preparation of pyrazolidin-3-ones **61** and isoxazolidin-5-ones **63** by treatment of the enonolactone **59** with hydrazine, hydroxylamine or their N-substituted derivatives, resulting from the spontaneous intramolecular cyclization of the Michael adducts **60** and **62** (Scheme 18).



Scheme 18. Michael addition of hydrazines and hydroxilamines (R = H, Me, Bn) to sugar enonolactone **59**, leading to pyrazolidin-3-ones and isoxazolidin-5-ones.

3. Sugars Containing α,β-Unsaturated Ketones

Like their lactone counterparts, carbohydrate-derived α,β-enones, namely cyclic derivatives, are versatile building blocks for the synthesis of natural products and have been employed for the generation of a diversity of chiral molecules. With respect to the naturally occurring enone-containing sugars, we can underline Vineomycin B2 [31], an anthracycline antibiotic, containing two hex-2-enosyl hexose disaccharide moieties, and the antioxidant Ascopyrone P (APP), a metabolite from fungi which displays antibacterial activity [32] (Fig. 2).



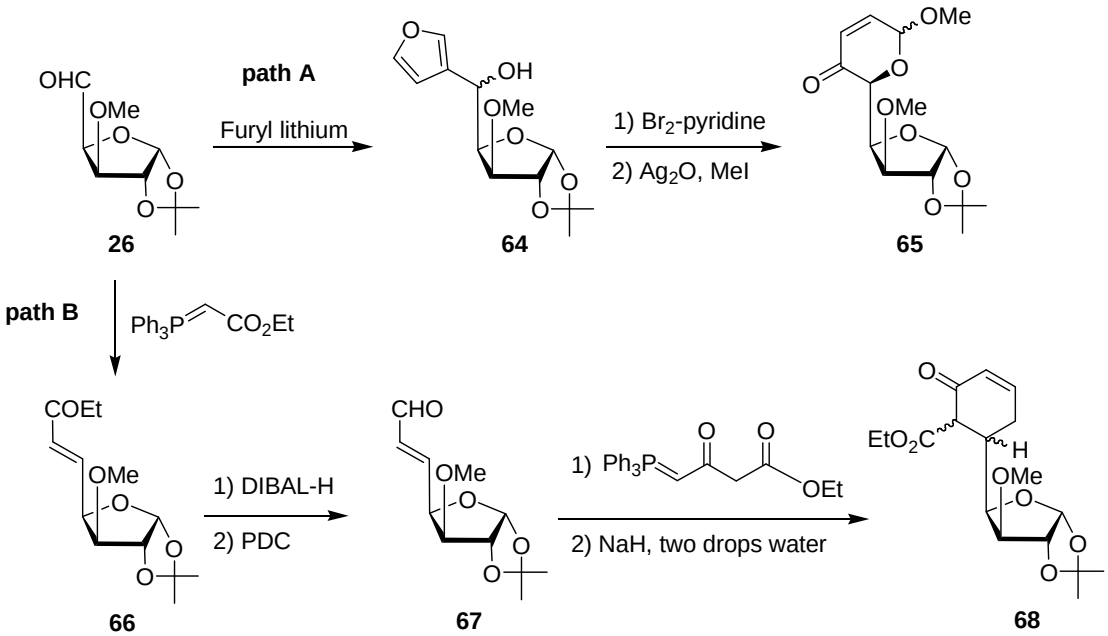
Vineomycin B_2 **APP**

Figure 2. Some naturally occurring α,β-enone-containing sugars.

3.1. α,β-Unsaturated Ketones Linked to Sugars

Concerning cyclic α,β-unsaturated ketones linked to sugars, only a few examples have been described in the literature, and those report mainly the use of these compounds as templates for the synthesis of C-C-linked disaccharides [33].

Two different approaches for C-C-linked disaccharides via α,β-enones, starting from dialdofuranoses, were developed by Sharma et al. [33]. In one of them (path A, Scheme 19), the sugar-linked enone was prepared by reaction of the aldehyde **26** with furyl lithium and further oxidation and methylation of the furanyl sugar-intermediate **64** [33a]. The second methodology (path B) consisted of the Wittig olefination of **26** to give the α,β-unsaturated ester **66,** which was subjected to DIBAL-H reduction and subsequent oxidation with pyridinium dichromate (PDC) to afford the enal **67** [33b]. The crucial [3+3] annulation reaction of **67** with ethyl 3-oxo-4-(triphenylphosphorylidene)butanoate in the presence of NaH and a drop of water resulted in the formation of sugar-linked α,β-enones **68** as a mixture of diastereoisomers. The desired dissacharides were obtained after enone reduction of **65** and **68**, followed by acetylation and *cis*-dihydroxylation.



Scheme 19. Synthesis of furanose-linked α,β-unsaturated ketones as templates for C-C-linked disaccharides.

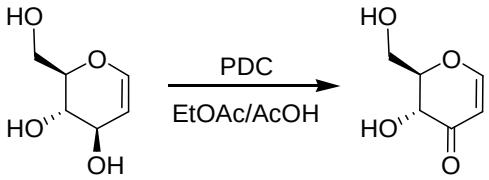
3.2. α,β-Unsaturated Pyranuloses

α,β-Unsaturated pyranuloses continue to serve as reliable scaffolds for the generation of branched-chain sugars and *C*-glycosyl derivatives, highlighted among a diversity of molecular targets.

Most of the methodologies to obtain α,β-unsaturated pyranuloses use readily available glycals as starting materials. It is not our intention to give an exhaustive coverage of the chemistry of pyranuloses (classical methods were reviewed in 1978 and 1982) [34] but rather to focus on the recent advances in the field, as well on the synthetic utility of these compounds, namely as universally reactive Michael addition acceptors.

3.2.1. 1-Enopyranos-3-uloses

Protected 1-enopyranos-3-uloses are of particular interest, mainly for their ability to allow chain extension at the anomeric carbon through 1,4-additions, leading to 2-deoxy-*C*-glycosyl derivatives after reduction of the resulting ketone at the position 3. The direct oxidation of allylic alcohols has actually become the most common method for the preparation of hex-1-enopyran-3-uloses. In 1986 Czernecki et al. described a convenient route to these sugar enones by selective oxidation of unprotected glycals with PDC, being the target compounds obtained as major products (Scheme 20) [35].



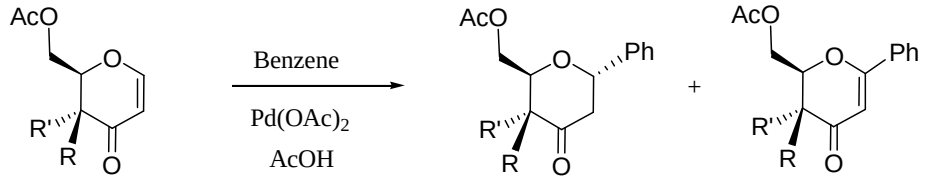
69 **70**

Scheme 20. Synthesis of the hex-1-enopyranos-3-ulose **70** by selective PDC oxidation of the unprotected glycal **69**.

Some years latter this research group reported the oxidation of the D-glycal **69** with a stoichiometric amount of $Pd(OAc)_2$ in aq. DMF [36]. In an alternative approach, $Pd(OAc)_2$ was used as a catalyst and the transformation carried out in the absence of

molecular oxygen. The reaction was performed under an ethylene atmosphere to avoid formation of the glycal reduced product, leading to the desired enones in good to excellent yields [37].

Palladium catalysts have also been used for further key transformations of hex-1-enopyranos-3-uloses, namely in C-glycosylation reactions. For example, treatment of peracetylated glycal-derived enones **71** with benzene in the presence of acetic acid and palladium acetate led to mixtures of 2-deoxy-*C*-glycopyranosyl derivatives **72** and arylated enones **73** (Scheme 21) [38].



71a R = H; R' = OAc
71b R= OAc; R' = H

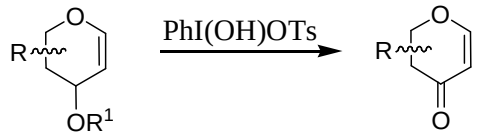
72a
72b

73a
73b

Scheme 21. Palladium-mediated arylation of hex-1-enopyranos-3-uloses.

In other research, acetylated and unprotected enones derived from the D-glycal **69** reacted via 1,4-addition with trimethylsilyl cyanide in the presence of a catalytic amount of a $Pd(OAc)_2$ to afford the corresponding 3-keto glycosyl cyanides. Heterogeneous catalysis (Pd/C) also worked in the cyanation reaction of **70** [39].

In extension to the unprotected glycals oxidation, the use of hypervalent iodine reagents for the oxidation of 3-*O*-protected derivatives has been developed [40]. In the work described by Kirschning et al., glycals **74,** containing different protective groups, were directly converted to the corresponding hex-1-enopyran-3-uloses **75** by [hydroxy(tosyloxy)iodo]benzene in the presence of molecular sieves (Scheme 22) [40a-b]. Moreover, the stereochemistry at C-3 in the starting material as well as the nature and the number of protecting groups on the pyran ring do not seem to be determinant factors for the reaction efficiency [40b].

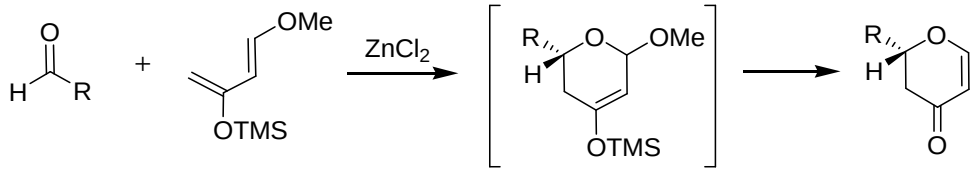


74a-d R^1 = Ac, Bn, MOM, SiR_3 **75a-d**

Scheme 22. Synthesis of the enopyranos-3-uloses by oxidation of fully protected glycals with [hydroxy(tosyloxy)iodo]benzene.

Another hypervalent iodine reagent used for the oxidation of 3-*O*-protected glycals to enopyranos-3-uloses is iodobenzene diacetate [$PhI(OAc)_2$] [40c].

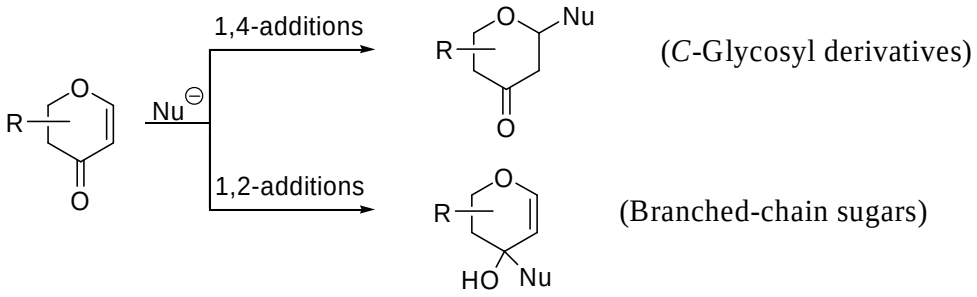
Besides glycal oxidation, other methods, such as cyclocondensation reactions of functionalized dienes with aldehydes, have been reported for the synthesis of enopyranos-3-uloses [41]. Danishefsky et al. described the Lewis acid catalyzed cycloadditions of siloxy dienes with aldehydes as a general route to these hexenuloses [41a]. Hence, reaction of diverse aldehydes with *trans*-l-methoxy-3-[(trimethyl)silyloxy]-1,3-butadiene **76** in the presence of zinc chloride afforded the desired enones **78**, which may arise via 1:l cycloadducts **77** (Scheme 23). These transformations were also carried out with boron trifluoride etherate as catalyst, followed by treatment with TFA.



76 **77** **78**

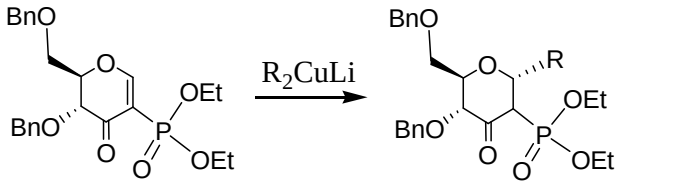
Scheme 23. Synthesis of the enopyranos-3-uloses **78** by cycloaddition of a silyloxy diene to aldehydes catalized by a Lewis acid.

1-Enopyranos-3-uloses are attractive starting materials for the formation of *C*-glycosyl derivatives and branched-chain sugars due to their tendency to undergo 1,4-additions or 1,2- additions (Scheme 24) [42].



Scheme 24. Nucleophilic additions to hex-1-enopyranos-3-uloses.

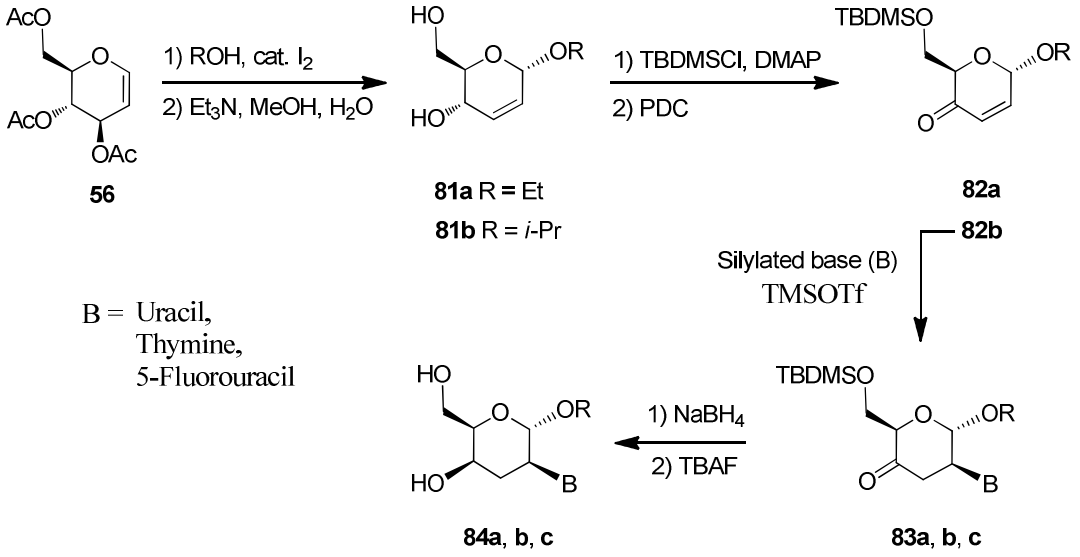
Michael-type additions of *O*- and *S*-nucleophiles to hex-l-en-3-uloses have been described using ZnI_2, DBU and KCN/18-crown-6 as catalysts to afford the corresponding ulosides in moderate yields [42a]. Recently, 2-deoxy-1-thio-α-hexopyranosid-3-uloses were synthesized with high diastereoselectivity by 1,4-addition of aryl and alkyl thiols to the enone system, promoted by cesium carbonate [42b]. Silyl- and sulfur-stabilized carbanions and their propensity to afford products of 1,2- or 1,4-additions, varying the combination of substituents attached to the C-l-anion, have also been studied [42c]. Conjugate addition of organometallic reagents to these heterocyclic enones, namely Grignard or organocopper reagents, and insights onto the reaction stereoselectivity have been reported [42d,e]. Leonelli et al. showed that Michael-type organocopper addition to 2-(diethoxyphosphoryl)hex-1-en-3-uloses (**79**) lead preferentially to α-anomers (Scheme 25) [42e]. These compounds can be direct precursors of 2-phosphono-α-*C*-glycosyl products **80**.



Scheme 25. Michael-type addition of organocopper reagents to 2-(diethoxyphosphoryl) hex-1-en-3-uloses **79** leading to **80**.

3.2.2. 2-Enopyranos-4-uloses

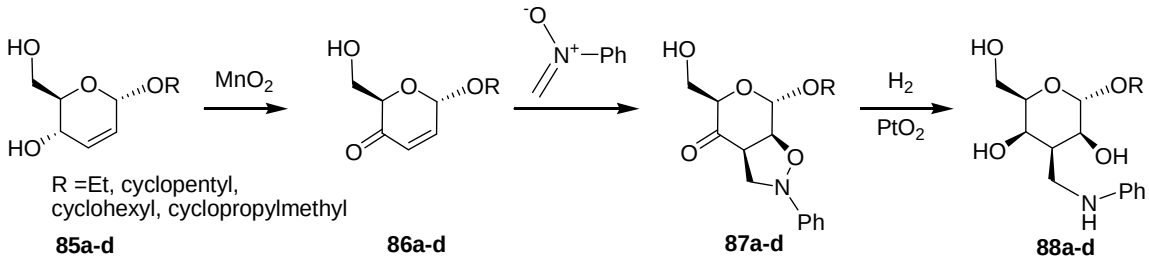
Due to their functionality, 2-enopyranos-4-uloses have been used as starting materials for nucleophilic additions [43] or cycloaddition reactions [44] to the double bond, and therefore for the generation of branched-chain sugars, isonucleosides or 3-deoxy-(1→2)-disaccharides. These enuloses are generally synthesized using the well-known Ferrier rearrangement of 3-*O*-acyl-glycals [45], followed by allylic oxidation at C-4 [34, 43b–c, 44b]. In the following example (Scheme 26), iodine catalized *O*-glycosylation of the glycal **56,** followed by hydrolysis, afforded unprotected 2,3-unsaturated glycosides **81** [43b]. The latter were selectively protected at the primary hydroxyl group, being the resulted silyl ethers subjected to PDC oxidation to furnish the hex-2-enopyranosid-4-uloses **82**. Compound **82b** was used for the preparation of new sugar-modified nucleosides by Michael-type addition of silylated bases in the presence of trimethylsilyl triflate as a Lewis acid. The thus obtained adducts **83** were submitted to reduction and desilylation to give the desired products **84**.



Scheme 26. Synthesis of hex-2-enopyranosid-4-uloses via 2,3-unsaturated pyranosides and their conversion into isonucleosides.

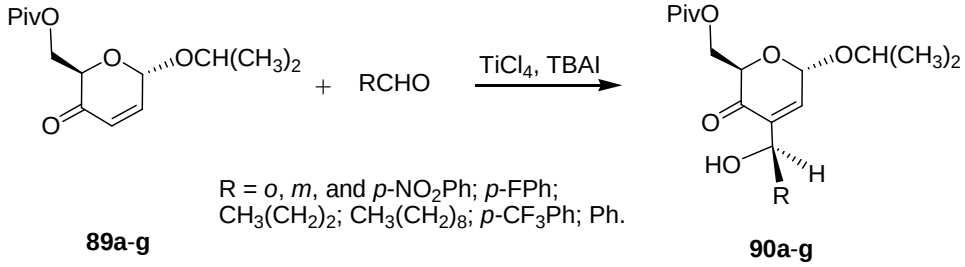
Alternatively, unprotected 2,3-unsaturated pyranosides can be directly converted to the corresponding 2-en-4-uloses by allylic oxidation with activated manganese dioxide, in good yields, as reported by de Freitas Filho et al. (Scheme 27) [44b]. The reported 1,3-

dipolar cycloaddition of methylideneaniline *N*-oxide to **86** occurred from the opposite side to the aglycone to afford the phenylisoxazolidin-4-uloses **87**. Hydrogenation of these compounds provided branched-chain amino sugars **88**, due to the simultaneous cleavage of the N-O bond of the isoxazolidine system and carbonyl reduction.



Scheme 27. Synthesis of hex-2-enopyranosid-4-uloses **86** by oxidation of unprotected 2,3-unsaturated pyranosides **85**, and their conversion into branched-chain amino sugars **88**.

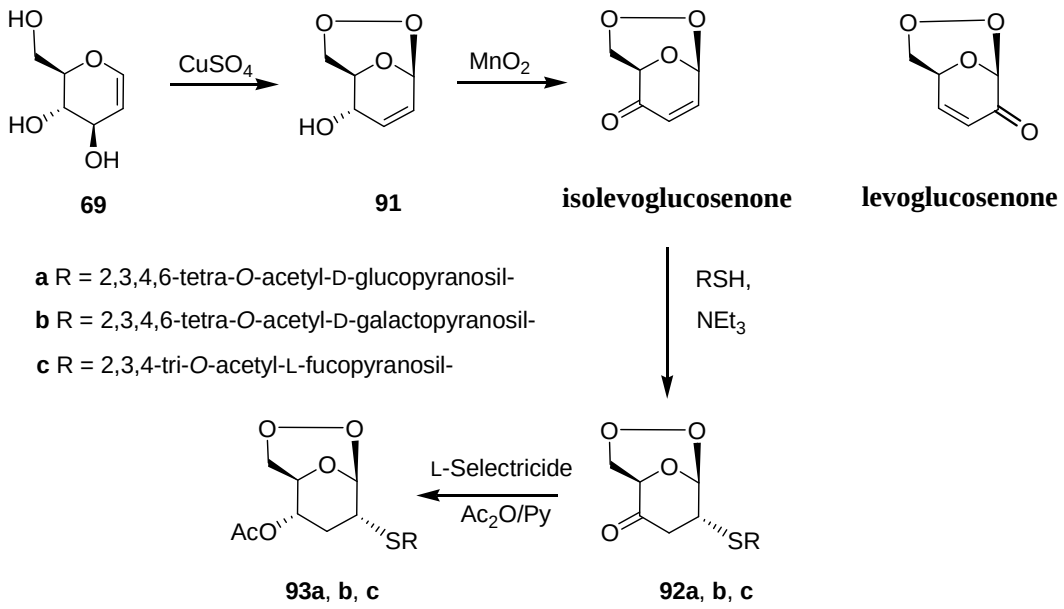
A different approach for the synthesis of 3-*C*-branched deoxy sugars from hex-2-enopyranosid-4-uloses was developed by Sagar et al. [46]. It consisted of the Morita–Baylis–Hillman (MBH) reaction [47] of various aldehydes with the enuloside **89** in the presence of $TiCl_4$ and TBAI (Scheme 28). By this procedure, *C*-3-alkylated 2,3-dideoxy sugars **90** were obtained in a diastereoselective manner in very good yields.



Scheme 28. Hex-2-enopyranosid-4-uloses as substrates for MBH reaction with aldehydes, leading to 3-*C*-branched deoxy sugars**.**

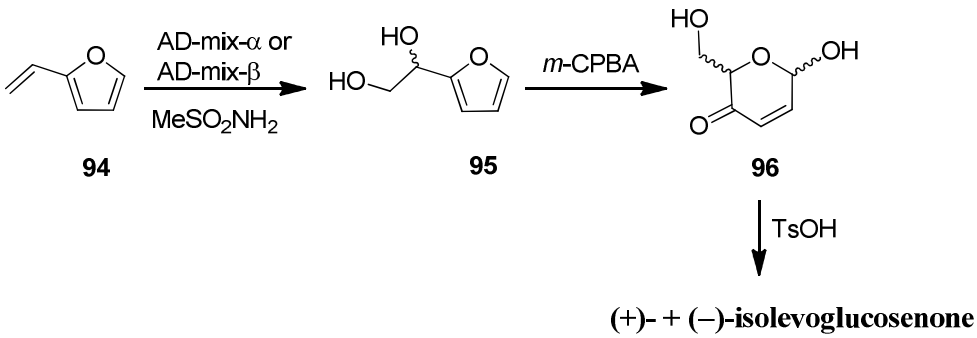
The fully unprotected glycal **69** was used by Witczak et al. as a suitable precursor of isolevoglucosenone, the hex-2-enopyranos-4-ulose isomer of levoglucosenone (Scheme 29) [43c]. This latter hex-3-enopyranosid-2-ulose is prepared by acid catalyzed pyrolysis of cellulose and can be a versatile scaffold for important sugar derivatives

[48]. Hence, Ferrier rearrangement of the unprotected D-glycal **69**, promoted by anhydrous copper sulfate and molecular sieves, resulted in the allyl alcohol **91**, which was subsequently oxidized with MnO_2 to give the target isolevoglucosenone [43c]. This compound could be then functionalized into 3-deoxy-(1→2)-2-*S*-thiodisaccharides **93** by base-catalyzed conjugate addition of 1-thiosugars, followed by reduction of the C-4 keto function of **92** with L-Selectride®.



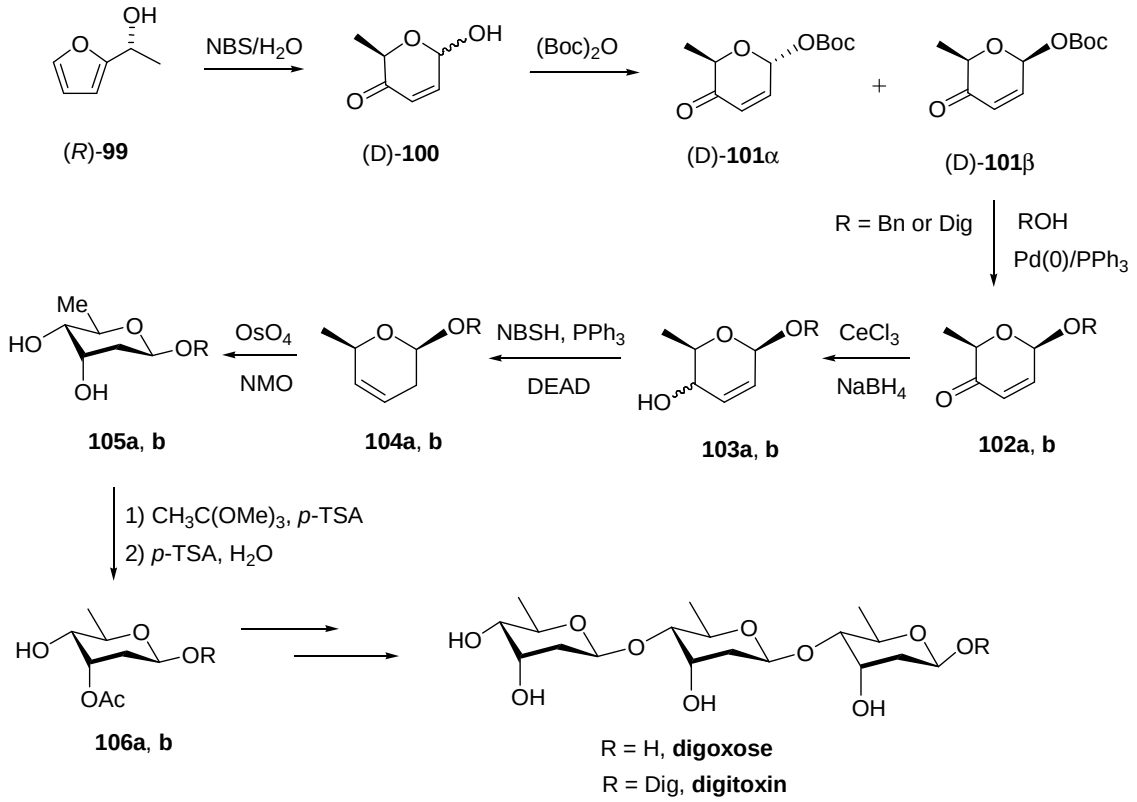
Scheme 29. Synthesis of isolevoglucosenone from the unprotected D-glycal **69** and Michael addition of 1-thiosugars to afford *S*-thiodisaccharides **93**.

Another methodology for the synthesis of hex-2-enopyranos-4-uloses involves the oxidation of non-carbohydrate furanyl alcohols [34, 48]. Ogasawara and co-workers made use of this approach for the preparation of isolevoglucosenone and its enantiomer [49]. For this purpose, 2-vinylfuran **94** was subjected to asymmetric dihydroxylation to give diols **95**, which were oxidized to enones **96** by treatment with *m*-CPBA. Dehydration of **96** in acidic medium provided the desired (+)- and (–)-isolevoglucosenones (Scheme 30).



Scheme 30. Synthesis of (+)- and (-)-isolevoglucosenone via oxidation of furanyl diol **95**.

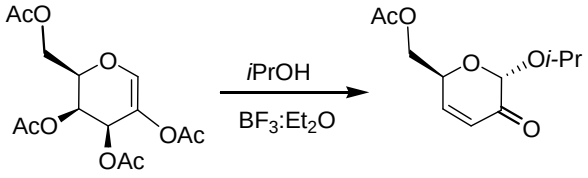
The oxidation of a furanyl alcohol was also employed by Zhou and O'Doherty [4a] for the preparation of hex-2-enopyranos-4-ulose **100**, which was a key compound for the synthesis of the already mentioned natural product digitoxin (Figure 1), a cardiac glycoside widely used for the treatment of congestive heart failure and cardiac arrhythmia [4], and its trisaccharide digoxose. In addition, digitoxin has been reported to possess potential anticancer activities [4d–g]. Hence, oxidation of the alcohol **99** gave the enulose **100**, which was then protected to the *tert*-butyloxycarbonyl esters **101** (Scheme 31). Palladium-catalyzed glycosylation of **101** β with benzyl alcohol or digitoxigenin (Dig), the aglycon of digitoxin, provided the glycosides **102**. The latter compounds were subjected to reduction to the corresponding allylic alcohols **103**, followed by reductive transposition to afford the alkenes **104**. Further dihydroxylation led to the diols **105,** which were regioselectively protected at the axial hydroxyl group by treatment with trimethyl orthoacetate in the presence of *p*-toluenesulfonic acid and subsequent acid hydrolysis. The synthetic pathway proceeded iteratively, with the same palladium-catalyzed glycosylation conditions of the resulting alcohols **106** with **101** β, followed by the same steps as described above, and allowing the generation of disaccharides and trisaccharides. The target molecules, digoxose and digitoxin, were obtained after removal of the benzyl and acetyl groups, respectively.



Scheme 31. Iterative synthesis of digoxose and digitoxin based on the Pd-catalyzed glycosylation reactions with hex-2-enopyranos-4-ulose **101** β.

3.2.3. 3-Enopyranos-2-uloses

3-Enopyranos-2-uloses comprise another class of α,β-unsaturated pyranuloses in which the α,β-unsaturated keto system can be generated by synthetic transformations on simple glycals with 2-hydroxy glycals generally used for this purpose. Varela and co-workers have made several contributions to this field [50]. An early straightforward procedure for the preparation of these compounds consisted of glycosylation of alcohols with 2-acyloxy-glycals (e.g., **107**) in the presence of a Lewis acid. The latter is, therefore, responsible for the double allylic rearrangement that occurs in the glycosylation reaction [50a]. Various catalysts have been used in such reactions, namely boron trifluoride diethyl etherate [50a] (Scheme 32) or tin(IV) chloride [50b,c].

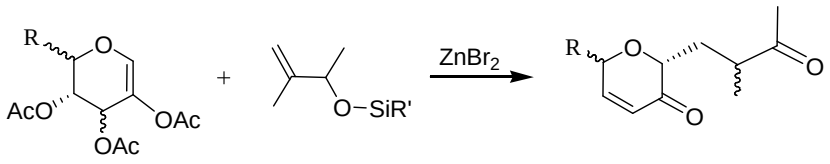


107 **108**

Scheme 32. Synthesis of hex-3-enopyranosid-2-ulose (**108**) by alcohol glycosylation with 2-acyloxy glycal (**107**) using boron trifluoride diethyl etherate as catalyst.

Iodine or electrophilic iodine-releasing agents such as *N*-iodosuccinimide also proved to be effective by mediating the glycosylation of alcohols with 2-hydroxyglycal esters to provide enopyranosiduloses [50d].

The synthesis of 2-keto α,β-unsaturated *C*-glycosyl derivatives has been described by Herscovici et al. [51] via reaction of peracetylated 2-hydroxy glycals with silyloxy allylic ethers. Condensation of several glycals (**109**) with hexyldimethylsiloxy ether in the presence of zinc bromide led stereoselectively to α-*C*-glycosyl compounds (**110**) (Scheme 33). Insights onto the mechanism of this transformation suggest an attack of the olefin to the glycal at C-1, followed by rearrangement of the resulting carbocation. Further acetolysis of the resulting 2-acetyloxy derivatives in the enol ester proceeded with the formation of the target enones [51a].



R = H, CH_2OAc

109a, **b**, **c**

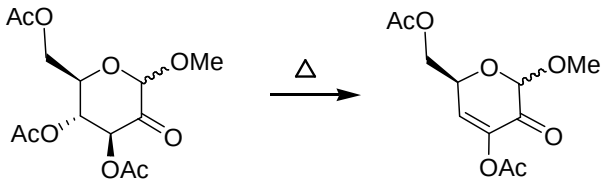
R' = Thexyl

110a, **b**, **c**

Scheme 33. Synthesis of 3-enopyranos-2-uloses (**110**) by reaction of 2-hydroxy glycals (**109**) with thexyldimethylsiloxy ether in the presence of $ZnBr_2$.

In addition to glycals, glycopyranosyl 2-uloses possessing an ester function at the position α to the carbonyl group, for example, **111** (Scheme 34) [52a], can be easily converted into 3-enopyranos-2-uloses (**112**). This arises from the keto–enol

tautomerism of the carbonyl compound followed by β-elimination, which frequently occurs spontaneously or under very mild conditions [52].

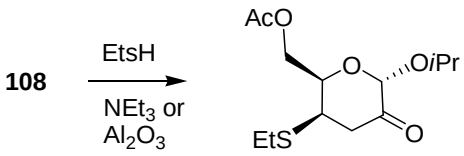


111 **112**

Scheme 34. Facile elimination of AcOH from 3-*O*-acetyl-2-uloside (**111**) to the corresponding enone (**112**).

The tendency for β-elimination was also found to be general in the oxidation of partially-protected sugars possessing a free primary or anomeric hydroxyl group, allowing the formation of a variety of α,β-unsaturated carbonyl sugar derivatives. In an early report by Mackie and Perlin [52c], oxidation of *O*-acyl and *O*-benzoyl protected hexopyranoses containing a free OH-6 with methyl sulfoxide in the presence of sulfur trioxide and triethylamine occurred with elimination either of the 4-acetoxy or the 4-benzoyloxy group to yield 4-deoxy-6-aldehydo-hex-4-enopyranoses. Under the same conditions, oxidation of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose afforded the corresponding pyranoid α,β-unsaturated δ-lactone.

3-Enopyranosid-2-uloses can undergo similar conjugate 1,4-addition reactions as previously discussed for the other classes of enuloses. Their usefulness as Michael acceptors has given rise to the formation of 3-deoxy-4-thiopyranosid-2-uloses such as **113** (Scheme 35), by addition of thiols to the enone system [53], being these compounds precursors of *C*-2-branched-chain 4-thiopyranosides [53a] or heteroanellated pyranosides [53c].

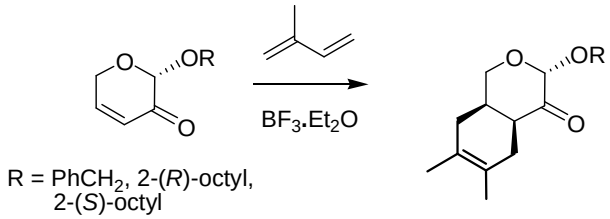


113

Scheme 35. Michael addition of ethanethiol to hex-3-enopyranosid-2-ulose **108**.

Michael addition to the important sugar precursor levoglucosenone has been reported [54]. One of the most attractive applications of these reactions has been the synthesis of thiodisaccharides [54b-f]. Witczak et al. [54b-c] described the stereoselective synthesis of 3-deoxy-4-*S*-(1→4)thiodisaccharides by Michael addition of 1-thiosugars to levoglucosenone. Analogous additions of per-*O*-acetyl-1-thioglucose to this substrate and other sugar enones have been studied by Thiem and co-workers [54d]. Synthesis of non-glycosidic 4,6´-thioether-linked disaccharides has also been developed, the key step of which was a highly diastereoselective Michael addition of a 6-thiohexopyranoside to a sugar enone [54f].

Diels-Alder cycloadditions of pent- or hex-3-enopyranosid-2-ulose with dienes, and studies related to their stereoselectivity have been published [50b-c,55]. Thus, the treatment of enones **114** with common dienes under thermal and Lewis acid catalyzed conditions led to bicyclic compounds **115** with diastereofacial selectivities (Scheme 36) [50b]. Noteworthy in these syntheses is the fact that these enones are better dienophiles than their cyclohexenones counterparts, which is probably due to the presence of the ring oxygen atom [50b]. Moreover, pent-3-enopyranosid-2-uloses exhibited higher activity than hexenuloses towards dienes [55a].

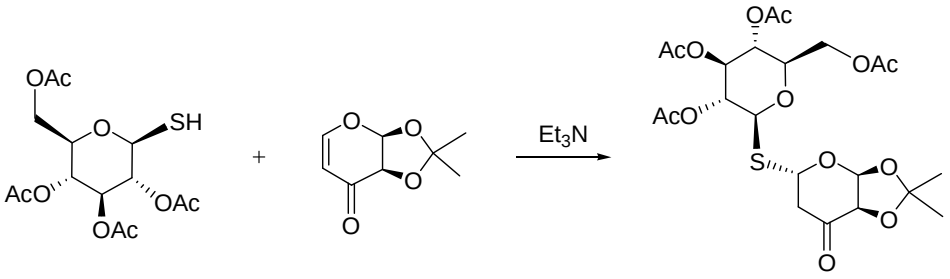


Scheme 36. Diels-Alder cycloadditions of pent-3-enopyranosid-2-uloses (**114**) with 2,3-dimethylbutadiene, catalized by boron trifluoride diethyl etherate.

3.2.4. 4-Enopyranos-3-uloses

Pent- or hex-4-enopyranos-3-uloses are practical scaffolds for preparing pyranosides containing a diversity of substituents at C-5, leading to 4-deoxy sugar derivatives.

Witczak et al. have recently explored the synthesis of 1,5-*C*-thiodisaccharides by Michael addition of a 1-thiosugar **116** to 4-deoxy-1,2-*O*-isopropylidene-L-*glycero*-pent-4-enopyranos-3-ulose (**117)** (Scheme 37) [56]. The reaction proceeded with the stereoselective formation of β-(1→5)-4-deoxy-5-*C*-thiodisaccharide **118** which results from the stereoselective nucleophilic attack at the less hindered face of the enone.



116 **117** **118**

Scheme 37. Stereolelective Michael addition of thiosugar **116** to pent-4-enopyranos-3-ulose **117** with formation of β-(1→5)-4-deoxy-5-*C*-thiodisaccharide **118**.

4. Conclusion

A remarkable amount of work has been reported during the last two decades towards the synthesis of α,β-unsaturated carbonyl sugar derivatives. The natural occurrence and the biological activities inherent to the α,β-unsaturated carbonyl moiety has been the driving force for several research groups to incorporate this functionality in carbohydrates. Furthermore, sugars containing α,β-unsaturated lactones or ketones have been attractive building blocks for natural products and new bioactive substances, as well as templates for key transformations due to the variety of reactions that the conjugated system may undergo. This review has illustrated recent advances on the synthesis of this type of compounds, as well as their significance in carbohydrate chemistry, demonstrated by the range of chemical targets they can provide.

Neverthless, as new apllications for α,β-unsaturated carbonyl carbohydrate-based compounds are found, the exploitation of novel synthetic and efficient methods for their preparation and transformation will continue to encourage the research in the area.

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2. Results and Discussion

2.1. Sugars Containing α,β-Unsaturated Lactones

The following subchapter includes the published papers concerning the synthesis of sugar derivatives containg butenolides, namely pyranose-fused butenolides and furanose C-C-linked butenolides. The biological activity of some of these molecules, namely their antifungal and antibacterial efficacy was also evaluated.

2.1.1. Pyranose-Fused Butenolides

This section includes the paper:

"Easy and Stereoselective Approach to α,β-Unsaturated-γ-Lactones Fused to Pyranoses from Furanose Scaffolds", Xavier, N. M.; Rauter, A. P. *Org. Lett.* **2007**, *9*, 3339−3341.

and shows the synthetic work on butenolides fused to pentopyranose or hexopyranose moieties.

The additional information contains the experimental details not described in this paper. It includes procedures reported in the paper given below, which was published to further establish the novelty of the work and the originality of these carbohydrate-based scaffolds:

Xavier, N. M.; Kopitzki, S.; Rauter, A. P., "Pyranose-Fused Butenolides: An Expedient Preparation from Furanose Synthons" in *Proven Synthetic Methods* (Ed. P. Kovac), Taylor & Francis, Boca Raton, Florida, **2010**, Vol. 1, in press.

The aim of *Proven Synthetic Methods* is to report simple, reliable and effective synthetic protocols in carbohydrate chemistry. Hence, the reproducibility of the method developed for pyranose-fused butenolides was verified by an external checker (Kopitzki, S.).

Org. Lett. **2007**, *9*, 3339−3341

Easy and Stereoselective Approach to α,β-Unsaturated-γ-Lactones Fused to Pyranoses From Furanose Scaffolds

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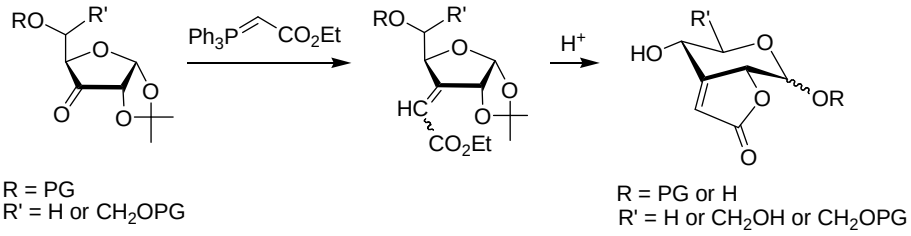
Abstract

The first facile and efficient route to pyranose-fused butenolides from furanose scaffolds, convenient for scaling up production, is described. Wittig olefination of 1,2-*O*-isopropylidene pentofuranos- or hexofuranos-3-uloses with a resonance stabilised ylide led to the stereoselective formation of the (*Z*)-α,β-unsaturated ester. In the presence of acid labile 5-*O*- or 5,6-di-*O*-protecting groups, acid hydrolysis of the Wittig product resulted in isomerisation to the pyranose form and spontaneous lactonization to give the target molecules in good overall yield.



The α,β-unsaturated γ-lactone motif is found in many natural products exhibiting a wide range of biological properties, namely, phytotoxic, antibacterial, or anti-inflammatory activities, with some of those compounds being described as potential anticancer agents, phospholipase A2 and cyclooxygenase inhibitors [1]. Furthermore, sugars comprising this structural moiety have been reported as fungicides or highly potent and selective insecticides (Figure 1) [2]. This biological profile encourages the search for efficient and straightforward approaches leading to new sugar based-butenolides.

Five-membered ring lactones fused to carbohydrate templates are known mainly in furanose systems. These compounds are useful intermediates for the preparation of nucleosides and branched-chain sugars [3]. Concerning sugar-fused α,β-unsaturated γ-lactones, only a few were reported, and those are fused to six-membered rings at positions 2 and 3 of the sugar [4]. However, their synthesis was implemented in a very low global yield using pyranos-2-uloses as starting materials, which are in general obtained in low yield by chemical synthesis.

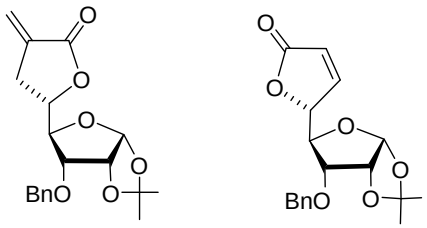
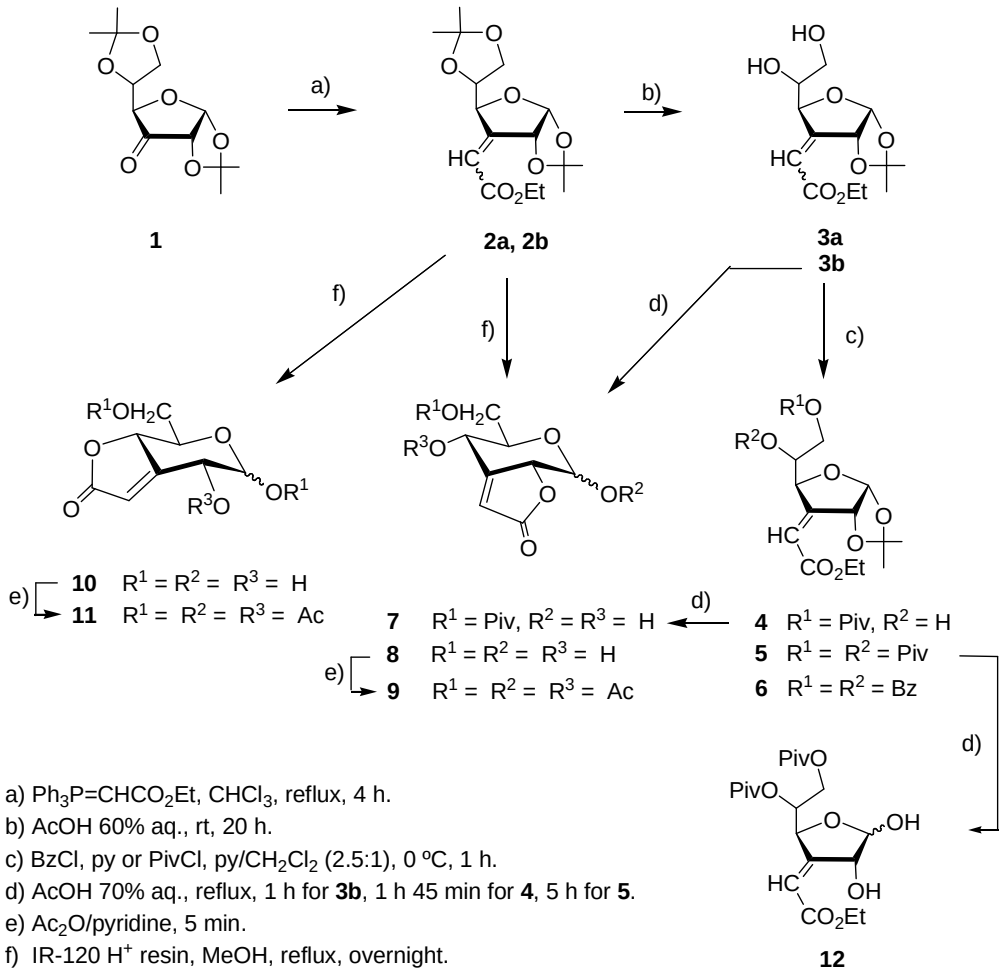


Figure 1. Structures of sugar-based α,β-unsaturated γ-lactones possessing fungicidal (A) and insecticidal properties (B).

We report herein an easy and direct method to prepare pyranose-fused butenolides starting from readily available pentofuranos- or hexofuranos-3-uloses.

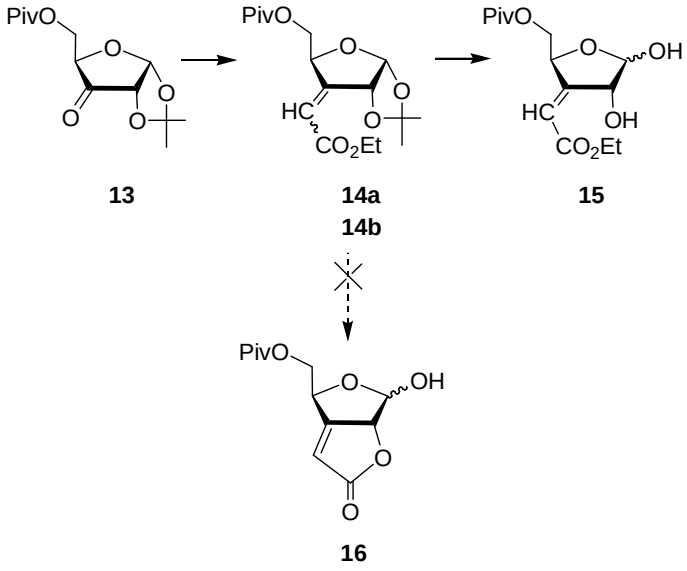
Butenolides fused to hexopyranoses were synthesized as illustrated in Scheme 1. The 3-keto sugar **1** was obtained by oxidation of commercially available 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose with PDC/Ac_2O in CH_2Cl_2 in nearly quantitative yield [5a], using a different workup than that described in the literature [5b]. It was subjected to Wittig reaction with [(ethoxycarbonyl)methylene]triphenylphosphorane in refluxing chloroform, affording the known (*E*)- and (*Z*)-α,β-unsaturated esters **2a** and **2b** [6], in 12% yield and 68% yield, respectively. The 5,6-*O*-isopropylidene group of **2b** was selectively removed by treatment with aq. acetic acid (60%) affording the 5,6-diol **3b** in 95% yield. Selective protection of the primary hydroxyl group of **3b** was successful even when the substate was treated with pivaloyl chloride in excess (2.4 equiv.) in py/CH_2Cl_2. The 6-*O*-pivaloyl derivative **4** was the major reaction product, isolated in 57% yield, and the 5,6-di-*O*-pivaloyl protected derivative **5** was obtained in only 27% yield. However, benzoylation afforded under similar conditions the 5,6-di-*O*-benzoyl derivative **6** in 83% yield, and no monoprotection was observed. The 6-*O*-

pivaloyl (*Z*)-α,β-unsaturated ester **4** was then submitted to hydrolysis with aq. acetic acid (70%) under reflux to give the target molecule **7** as a mixture of both anomers (α/β ratio 1:0.7) in 83% yield, resulting from deprotection of the 1,2-acetonide, furanose ring opening, its closure into the pyranose form, and intramolecular lactonization, in one single step. When compound **3b** was subjected to similar hydrolytic conditions, followed by acetylation with Ac_2O in pyridine, the triacetate derived-butenolide **9** was obtained in 78% overall yield (ratio α/β, 2:1). Direct synthesis of the intermediate deprotected butenolide **8** was successfully and readly achieved (90% yield) by acid hydrolysis of **2b** with IR-120 H^+ resin [7] in refluxing methanol (ratio α/β, 3:1). Moreover, the butenolide fused to positions 3 and 4 of a pyranose moiety **10** was successfully obtained by resin acid hydrolysis of the (*E*)-α,β-unsaturated ester **2a**, which after acetylation gave the triacetate derivative **11** as a 1:1 mixture of α,β-anomers in 63% yield overall yield.



Scheme 1.

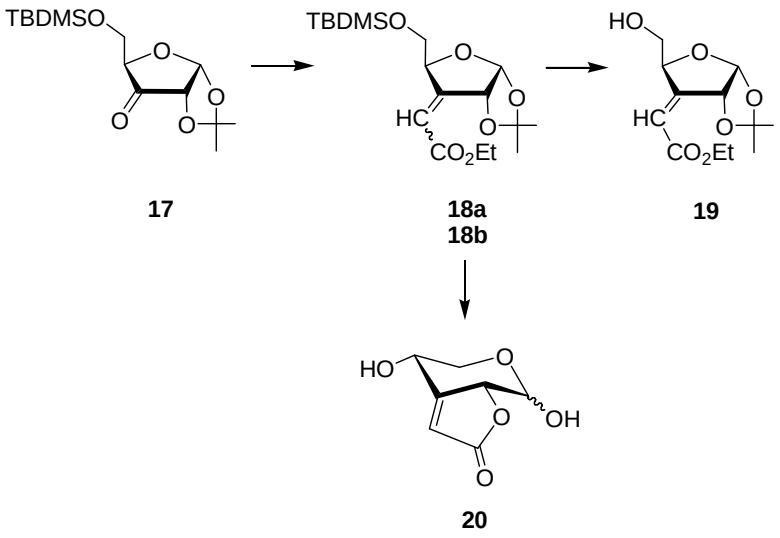
However, no intramolecular cyclization was observed by removal of the 1,2-*O*-isopropylidene group of **5**, which comprises a nonacid labile and bulky pivaloyl protecting group at position 5, being the 1,2-diol **12** isolated in 62% yield. This result suggests that the formation of butenolides 2,3-fused to carbohydrates under these experimental conditions is favored in pyranose systems rather than in furanose forms. Confirmation of this finding was possible when the pentofuranosid-3-ulose **13** [18] (Scheme 2), with the acid resistant 5-*O*-pivaloyl group, was used as starting material. Its synthesis was accomplished by PDC/Ac_2O oxidation of 1,2-*O*-isopropylidene -5-*O*-pivaloyl-α-D-xylofuranose [9] in 81% yield. Wittig olefination of **13** was stereoselective, leading to the (*Z*)-α,β-unsaturated ester **14b** in 70% yield, with the (*E*)-adduct **14a** being isolated in 12% yield. As expected, intramolecular lactonization to **16** did not occur by treatment with aq. acid acetic, resulting in the 1,2-diol **15** in 70% yield (ratio α/β, 1:0.7), thereby reinforcing that butenolides are difficult to fuse at positions 2,3 of furanose rings with this methodology.



Scheme 2.

The preparation of butenolides 2,3-fused to pentopyranose units (Scheme 3) was accomplished following a synthetic pathway similar to that described above for the hexopyranose moieties. The primary hydroxyl group of 1,2-*O*-isopropylidene-α-D-xylofuranose, easily prepared from D-xylose and commercially available, was selectively protected with the acid labile *tert*-butyldimethylsilyl group in quantitative

yield, the resulting silyl ether being oxidized to the pentofuranos-3-ulose derivative **17** [10] with PDC/Ac_2O for the first time, in 97% yield. When this 3-keto sugar reacted with [(ethoxycarbonyl)methylene]triphenylphosphorane in chloroform under reflux, stereoselectivity to the (*Z*)-α,β-unsaturated ester **18b** [11] was achieved, with this isomer being isolated in 81% yield and the (*E*)-isomer being obtained in 8% yield. Selective hydrolysis of **18b** with aq. acid acetic (70%) at 70 ºC afforded the desilylated derivative **19** in 85% yield, and IR-120 H^+ resin promoted total hydrolysis with the formation of the butenolide 2,3-fused to the pentopyranose ring **20** in 79% yield in a 1:1 mixture of the α,β-anomers.



Scheme 3.

In conclusion, a reliable and facile method is described for the stereoselective synthesis of potentially bioactive carbohydrate-based butenolides fused to pento- and hexopyranose rings. The synthetic strategy followed herein involves a short number of steps leading to the target molecules in good overall yield, with the added value of a possible regioselective protection for further derivatization. The readily avaliable starting materials obtained from inexpensive sugars (D-glucose and D-xylose) and the easy and efficient experimental procedures, make this methodology useful for the preparation of new sugar derivatives of biological interest.

Acknowledgment. The authors thank Fundação para a Ciência e Tecnologia for the financial support of the project POCI/AMB/58116/2004.

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[5] (a) **General experimental procedure for PDC/Ac_2O oxidation**: A solution of sugar (3.47 mmol) in dry CH_2Cl_2 (6 mL) was added to a mixture of PDC (0.96 g, 2.57 mmol) and Ac_2O (1.1 mL, 11.6 mmol) in dry CH_2Cl_2 (12 mL) under argon. The resulting mixture was stirred under reflux until complete conversion, then cooled to room temp. The solvent was removed in vacuo. Diethyl ether (50 mL) was added to the solid residue, and the mixture was filtered over Florisil. The solvent was removed under vacuum to afford the 3-keto sugar; (b) Lee, J..-C., Chang, S.-W., Liao, C.-C., Chi, F.-C. Chen, C.- S., Wen, Y.-S., Wang, C.-C., Kulkarni, S. S., Puranik, R., Liu, Y.-H., Hung, S.-C. *Chem. Eur. J.* **2004**, *10*, 399–415.

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[7] **Typical experimental procedure for IR-120 H^+ resin promoted hydrolysis:** To a solution of 3-deoxy-3-C-[(*Z*)-(ethoxycarbonyl)methylene]- 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranose (0.11g, 0.33 mmol) in MeOH (1.8 mL) was added Amberlite IR-120 H^+ resin (35 mg). The mixture was moderately stirred under reflux overnight. After filtration of the resin and evaporation of the solvent, the crude

product was purified by CC on silica-gel using AcOEt as eluent to afford 8 (60 mg, 90 %) as a white solid.

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Additional Information to *Org. Lett.* 2007, *9*, 3339−3341

The conversion of **2a** into **8** could also be carried out using an aq. TFA solution (60%) in 5 min and 90% yield.

Experimental

General methods and procedures as well as full characterization of compounds **1**, **2a**, **2b**, **3a**, **4**, **5**, **7**, **8**, **9**, **17**, **18a**, **18b** and **20** published in:

Xavier, N. M.; Kopitzki, S.; Rauter, A. P., "Pyranose-Fused Butenolides: An Expedient Preparation from Furanose Synthons" in *Proven Synthetic Methods* (Ed. P. Kovac), Taylor & Francis, Boca Raton, Florida, **2010**, Vol. 1, in press.

General Methods: 1,2:5,6-di-*O*-Isopropylidene-α-D-glucofuranose (DAG) and 1,2-*O*-isopropylidene-α-D-xylofuranose were purchased from Sigma-Aldrich. Melting points were determined with a Stuart Scientific SMP 3 apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 343 polarimeter at 20 ºC. ^{1}H and ^{13}C NMR spectra were recorded with a BRUKER Avance 400 spectrometer operating at 400.13 MHz for ^{1}H or 100.62 MHz for ^{13}C. Chemical shifts are expressed in parts per million and are reported relative to internal TMS or relative to the respective solvent peak. Signal assignments were made with the help of DEPT, COSY, HMQC and HMBC experiments. HRMS spectra were acquired with an Apex Ultra FTICR Mass Spectrometer equipped with an Apollo II Dual ESI/MALDI ion source (Bruker Daltonics), and a 7T actively shielded magnet (Magnex Scientific). Elemental analyses were performed at the Microanalyses Service of Instituto Superior Técnico-Universidade Técnica de Lisboa.

All reactions were monitored by TLC on Merck 60 F_{254} silica gel-coated aluminium plates with detection under UV light (254 nm) and/or by charring with 10% H_2SO_4 in EtOH. Column chromatography (CC) was performed on silica gel 60 G (0.040–0.063 mm, E. Merck). Concentration of solutions was done at reduced pressure.

1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranosid-3-ulose (1): A solution of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (4.00 g, 15.4 mmol) in dry CH_2Cl_2 (24 mL) was added under argon to a mixture of PDC (4.32 g, 11.4 mmol) and Ac_2O (4.4 mL, 46.5 mmol) in dry CH_2Cl_2 (48 mL). The mixture was stirred under reflux for 2 h, cooled to room temp. and concentrated. The gummy residue was triturated with Et_2O (3×150 mL), and the ethereal extract was filtered through Florisil. The eluate was concentrated to afford the title compound (3.78 g, 95%) as a colorless oil. R_f = 0.37 (EtOAc/petroleum ether, 2:3).^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.15 (d, 1H, H-1, $J_{1,2}$ = 4.3 Hz), 4.42-4.34 (m, 3H, H-2, H-4, H-5), 4.06-4.01 (m, 2 H, H-6a, H-6b), 1.46 (s, 3H, Me, isopr.), 1.44 (s, 3H, Me, isopr.), 1.34 (s, 6H, 2 × Me, isopr.) ppm.

3-Deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]- 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (2a) and 3-deoxy- 3-*C*-[(*E*)-(ethoxycarbonyl)methylene]-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (2b):

[(Ethoxycarbonyl)methylene]triphenylphosphorane (5.23 g, 15 mmol) was added to a solution of 3-ulose **1** (2.27 g, 8.78 mmol) in dry $CHCl_3$ (70 mL), and the mixture was stirred under reflux for 2 h. After concentration, the residue was chromatographed (EtOAc/petroleum ether, 1:9) to afford **2**-(*Z*) as a white solid (1.70–1.95 g, 59–68%) and its (*E*)-isomer as a colorless oil (0.34 g, 12%). Physical data were in agreement with those reported [6b].

Data for 2a: R_f = 0.27 (EtOAc/cyclohexane, 1:9). m. p. 68–70 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.34 (br. d, 1 H, H-3'), 5.85 (d, 1 H, H-1 $J_{1,2}$, = 4.3 Hz,), 5.75 (brd, 1H, H-2), 4.68 (brdd, 1H, H-4), 4.25 (q, 2H, CH_2CH$_3$, J = 7.1 Hz), 4.13-3.98 (m, 3H, H-5, H-6a, H-6b), 1.50, 1.45, 1.41, 1.37 (4 s, 4 × 3H, 4 × Me, isopr.), 1.32 (t, 3H, CH$_2$CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1 (*C*O), 155.7 (C-3), 117.9 (C-3'), 112.8, 110.1, (2 × Cq, isopr.), 104.9 (C-1), 79.9 (C-4), 78.4 (C-2), 76.8 (C-5), 67.3 (C-6), 60.7 (*C*H$_2$CH$_3$), 27.3, 27.1, 26.7, 25.4 (4 × Me), 14.2 (CH$_2$*C*H$_3$) ppm.

Data for 2b: R_f = 0.35 (EtOAc/cyclohexane, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.23 (br. d, 1 H, H-3'), 5.94 (d, 1H, H-1, $J_{1,2}$ = 4.8 Hz), 5.76 (brd, 1H, H-4), 5.11 (brdd, 1H, H-2), 4.35 (ddd, 1H, H-5, $J_{4,5}$ = 2.3 Hz), 4.19 (qd, 2H, CH_2CH$_3$), 3.97 (dd, 1H, H-6a, $J_{5,6a}$ = 6.3 Hz), 3.57 (t, 1H, H-6b, $J_{6a,6b}$ = 8.6 Hz,), 1.43, 1.39, 1.33, 1.32 (4 s, 4 × 3 H, 4 × Me, isopr.), 1.31 (t, 3H, CH$_2$CH_3, J = 7.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6 (*C*O), 158 (C-3), 118.1 (C-3'), 113.7, 109.1 (2 × Cq, isopr.), 103.8 (C-1), 82.3

(C-2), 80.0 (C-4), 79.0 (C-5), 65.4 (C-6), 60.8 (CH_2CH_3), 27.9, 27.9, 26.2, 25.7 (4 × Me), 14.2 (CH_2CH_3) ppm.

3-deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranose (3a): A solution of 3-deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**2a**, 0.79 g, 2.41 mmol) in aq. AcOH (60%, 9.6 mL) was stirred at room temp. for 20 h. The mixture was concentrated, the residue was co-evaporated with toluene (3×) and the crude product was chromatographed (EtOAc/petroleum ether, 2:3) to afford the title compound as a colorless oil (0.66 g, 95%). R_f = 0.25 (EtOAc/petroleum ether, 2:3). $[\alpha]_D^{20}$ = +165 (c = 1.2, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.30 (br. dd, 1H, H-3'), 5.87 (d, 1H, H-1, $J_{1,2}$ = 4.0 Hz), 5.73 (brd, 1H, H-2), 4.80 (br. d, 1H, H-4), 4.24 (q, 2H, CH_2CH$_3$), 3.79-3.70 (m, 3H, H-5, H-6a, H-6b), 1.49 (s, 3H, Me, isopr.), 1.41 (s, 3H, Me, isopr.), 1.31 (t, 3H, CH$_2$CH_3, J = 7.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3 (*C*O), 155.7 (C-3), 117.6 (C-3'), 113.0 (Cq, isopr.), 104.8 (C-1), 79.9 (C-4), 78.4 (C-2), 73.5 (C-5), 63.4 (C-6), 60.9 (CH_2CH_3), 27.3 (Me, isopr.), 27.2 (Me, isopr.), 14.2 (CH_2CH_3) ppm.

3-Deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-6-*O*-pivaloyl-α-D-*ribo*-hexofuranose (4) and 3-deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-5,6-di-*O*-pivaloyl-α-D-*ribo*-hexofuranose (5): A solution of pivaloyl chloride (2.12 mmol, 0.26 mL) in dry CH_2Cl_2 (1 mL) was added under argon to a solution of 3-deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**3a**, 0.24 g, 0.85 mmol**)** in dry pyridine (2.5 mL). The solution was stirred at room temp. for 1 h and concentrated. The residue was partitioned between water (10 mL) and CH_2Cl_2 (3 × 5 mL). Organic layers were washed with a sat. aq. $NaHCO_3$ solution, water and brine, and dried over $MgSO_4$. After filtration and evaporation of the solvent, the residue was chromatographed (EtOAc/cyclohexane, 1:4) to afford **6** and **7** as white solids [0.18 g (57 %) and 0.10 g (27%), respectively].

Data for 4: R_f = 0.35 (EtOAc/cyclohexane, 1:4). $[\alpha]_D^{20}$ = +87 (c = 0.8, in CH_2Cl_2). m.p. 97−99 °C (cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.32 (br. s, 1 H, H-3'), 5.88 (d, 1H, H-1, $J_{1,2}$ = 4.3 Hz), 5.74 (brd, 1H, H-2), 4.78 (brd, 1H, H-4, $J_{4,5}$ = 6.6 Hz), 4.33, 4.32, 4.30, 4.29 (dd, part AX of ABX system, 1H, H-6a, $J_{5,6a}$ = 3.0 Hz, $J_{6a,6b}$ = 11.6 Hz),

4.27-4.21 (m, 3H, H-6b, C*H*$_2$CH$_3$), 3.89 (ddd, H-5), 2.79 (d, OH-5, $J_{5,OH}$ = 3.8 Hz), 1.49 (s, 3 H, Me, isopr.), 1.42 (s, 3H, Me, isopr.), 1.31 (t, 3H, CH$_2$C*H*$_3$, J = 7.1 Hz), 1.22 (9H, Me, Piv) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ 179.4 (*C*O, Piv), 165.2 (*C*O), 155.3 (C-3), 117.9 (C-3'), 113.0 (Cq, isopr.), 105.0 (C-1), 79.6 (C-4), 78.5 (C-2), 72.3 (C-5), 65.8 (C-6), 60.8 (*C*H$_2$CH$_3$), 39.0 (Cq, Piv), 27.5 (Me, isopr.), 27.3 (Me, isopr.), 27.3 (Me, Piv), 14.3 (CH$_2$*C*H$_3$) ppm. Anal. Cald for $C_{18}H_{28}O_8$: C, 58.05; H, 7.58. Found: C, 57.92; H, 7.91.

Data for 5: R_f = 0.24 (EtOAc/cyclohexane, 1:9). $[\alpha]_D^{20}$ = +91 (c = 0 1, in CH$_2$Cl$_2$). m.p. 94−96 ºC (hexane). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.03 (t, 1H, H-3'), 5.89 (d, 1H, H-1, $J_{1,2}$ = 4.3 Hz), 5.72 (brd, 1H, H-2), 5.12 (ddd, 1H, H-5), 4.98 (brd, 1H, H-4), 4.34, 4.33, 4.31, 4.30 (dd, part AX of ABX system, 1H, H-6a, $J_{5,6a}$ = 3.0 Hz, $J_{6a,6b}$ = 12.1 Hz), 4.28-4.15 (m, 3H, H-6b, C*H*$_2$CH$_3$, $J_{5,6b}$ = 6.8, J = 7.1 Hz), 1.48 (s, 3H, Me, isopr.), 1.43 (s, 3H, Me), 1.30 (t, 3H, CH$_2$C*H*$_3$), 1.23 (9H, Me, Piv), 1.18 (9H, Me, Piv) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 178.1 (*C*O, Piv), 177.6 (*C*O, Piv), 164.6 (*C*O), 154.4 (C-3), 118.1 (C-3'), 113.2 (Cq, isopr.), 105.2 (C-1), 78.8 (C-4), 78.3 (C-2), 72.4 (C-5), 62.0 (C-6), 61.0 (*C*H$_2$CH$_3$), 39.0 (Cq, Piv), 38.9 (Cq, Piv), 27.5 (Me, isopr.), 27.3 (Me, isopr.), 27.2 (Me, Piv), 27.2 (Me, Piv) 14.2 (CH$_2$*C*H$_3$) ppm. Anal. Cald for $C_{23}H_{36}O_9$: C, 60.51; H, 7.95. Found: C, 60.48; H, 8.39.

3-*C*-(Carboxymethylene)-3-deoxy-6-*O*-pivaloyl-D-*ribo*-hexopyranose-3',2-lactone (7): A solution of 3-deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-6-*O*-pivaloyl-α-D-*ribo*-hexofuranose (**4**, 0.08 g, 0.22 mmol) in aq. AcOH (70%, 1.2 mL) was stirred under reflux for 1 h 45 min. After concentration, the residue was coevaporated with toluene (3×) and the crude product was chromatographed (EtOAc/petroleum ether, 3:2) to afford the title compound as a colorless oil (51 mg, 83 %). R_f = 0.33 (EtOAc/petroleum ether, 3:2). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 6.13 (br. s, H-3'), 5.66 (d, H-1*α*, $J_{1,2(\alpha)}$ = 4.2 Hz), 4.88 (dd, H-2α, $J_{2,3'(\alpha)}$ = 1.3 Hz), 4.67 (dd, H-2β, $J_{1,2\ (\beta)}$ = 7.1, $J_{2,3'\ (\beta)}$ = 1.3 Hz), 4.57-4.47 (m, H-1β, H-6aα, H-6aβ, $J_{5,6a\ (\alpha)}$ = 3.5 Hz, $J_{6a,6b\ (\alpha)}$ = 12.5 Hz), 4.46-4.35 (m, H-6bα, H-4α, H-4β, H-6bβ), 3.97 (ddd, H-5α), 3.47 (ddd, H-5β), 1.23 (s, Me, Piv, α, Me, Piv, β) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 180.0 (*C*O, Piv, β), 179.8 (*C*O, Piv, α), 174.3 (*C*O, lact., α), 173.6 (*C*O, lact., β), 169.3 (C-3β), 168.0 (C-3α), 113.8 (C-3'α, C-3'β), 99.0 (C-1β), 90.9 (C-1α), 82.4 (C-2β), 79.1 (C-2α), 78.2 (C-5β), 72.2 (C-5α), 67.2 (C-4β), 66.9 (C-4α), 62.9 (C-6β), 62.7 (C-6α),

39.2 (Cq, Piv), 27.3 (Me, Piv) ppm. HRMS: calcd. for $C_{13}H_{18}O_7$ $[M + H]^+$ 287.1125, found 287.1127; calcd. for $[M + Na]^+$ 309.0945, found 309.0947; calcd. for $[M + K]^+$ 325.0684, found 325.0684.

3-*C*-(Carboxymethylene)-3-deoxy-D-*ribo*-hexopyranose-3',2-lactone (8): Amberlite IR-120 H^+ resin (100 mg) was added to a solution of 3-deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**2a**, 0.3 g, 0.913 mmol) in MeOH–H_2O (5:1, 12 mL). The mixture was gently stirred under reflux for 16 h, the resin was filtered and the solvent was evaporated. The crude product was chromatographed using AcOEt as eluent to afford **4** as a white solid (165 mg, 90%). R_f = 0.22 (EtOAc). m.p. 168−174 ºC (AcOEt). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.56 (d, OH-1β, J = 5.6), 7.04 (d, OH-1α, J = 4.6 Hz), 6.00 (d, OH-4β, J = 5.8 Hz), 5.95-5.87 (m, H-3'α, H-3'β, OH-4α), 5.47 (t, H-1α), 4.96 (d, H-2α, $J_{1,2\ (\alpha)}$ = 4.1 Hz), 4.89 (t, OH-6β), 4.79 (t, OH-6α), 4.65 (d, H-2β, $J_{1,2\ (\beta)}$ = 7.1 Hz) 4.37-4.30 (m, H1-β, H-4α, H-4β), 3.79-3.52 (m, H-6aα, H-6aβ, H-6bα, H-6bβ, H-5α, $J_{5,6a\ (\beta)}$ = 5.3 Hz, $J_{6a,6b\ (\beta)}$ = 12.1 Hz, $J_{5,6a\ (\alpha)}$ = 5.3 Hz, $J_{6a,6b\ (\alpha)}$ = 11.6 Hz) 3.12 (ddd, H-5β) ppm. ^{13}C NMR (100 MHz, [D6]DMSO): δ = 172.9, 172.6, 172.4 171.1 (*C*O-α, *C*O-β, C-3α, C-3β), 111.7 (C-3'α, C-3'β), 98.7 (C-1β), 90.4 (C-1α), 82.0 (C-2β), 80.2 (C-5β), 78.6 (C-2α), 74.4 (C-5α), 66.1 (C-4β), 65.7 (C-4α), 60.1 (C-6α, C-6β) ppm. HRMS: calcd. for $C_8H_{10}O_6$ $[M + H]^+$ 203.0550, found 203.0550; calcd. for $[M + Na]^+$ 225.0370, found 225.0369; calcd. for $[M + K]^+$ 241.0109, found 241.0109. Anal. Cald. for $C_8H_{10}O_6$: C, 47.53; H, 4.99. Found: C, 47.60; H, 4.90.

Alternative Method for the conversion of 2a into 8 (*unpublished*):

A solution of 3-deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**2a**, 0.17 g, 0.51 mmol) in aq. TFA (60%, 3.4 mL) was stirred at room temp. for 5 min. The mixture was concentrated, the residue was co-evaporated with toluene (3×) and the crude product was cristalized from EtOAc to afford compound **8** as white solid (91mg, 90%).

1,4,6-Tri-*O*-acetyl-3-*C*-(carboxymethylene)-3-deoxy-D-*ribo*-hexopyranose-3',2-lactone (9): A solution of 3-deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**3a**, 0.07 g, 0.23 mmol) in aq. AcOH (70%, 1.2 mL) was stirred under reflux for 1 h. After concentration, Ac_2O (1 mL) and py (2 mL)

were added to the residue and the mixture was stirred for 5 min. After coevaporation with toluene (3×), the crude product was chromatographed (EtOAc/petroleum ether, 1:1) to afford the title compound as a colorless oil (0.06 g, 78 %). R_f = 0.32 (EtOAc/petroleum ether, 1:1). $[\alpha]_D^{20}$ = +178 (c = 1.2, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.60 (d, H-1α, $J_{1,2}$ = 4.6 Hz), 6.02-5.96 (m, H-3'α, H-3'β), 5.71 (dd, H-4α, $J_{3',4\,(\alpha)}$ = 1.5, $J_{4,5\,(\alpha)}$ = 9.6 Hz,), 5.66 (dd, H-4β, $J_{3',4\,(\beta)}$ = 1.5, $J_{4,5\,(\beta)}$ = 9.6 Hz), 5.40 (d, H-1β, $J_{1,2\,(\beta)}$ = 7.6 Hz), 5.10 (dd, H-2α, $J_{2,3'\,(\alpha)}$ = 1.5 Hz), 4.90 (dd, H-2β, $J_{2,3'(\beta)}$ = 1.5 Hz), 4.40-4.32 (m, H-6aα, H-6aβ) 4.28-4.19 (m, H-6bα, H-6bβ), 4.00 (ddd, H-5α), 3.77 (ddd, H-5β), 2.22 (s, Me, Ac, α, Me, Ac, β), 2.21 (s, Me, Ac, β), 2.11 (s, Me, Ac, α, Me, Ac, β), 2.09 (s, Me, Ac, α) ppm.^{13}C NMR ($CDCl_3$): δ = 171.0 (*C*O, Ac, α), 170.6 (CO, Ac, β, *C*O, lact., α, *C*O, lact., β), 169.1 (*C*O, Ac, β), 169.1 (*C*O, Ac, α), 168.7 (*C*O, Ac, β), 168.2 (*C*O, Ac, α), 163.2 (C-3β), 161.6 (C-3α), 115.3 (C-3'α), 114.7 (C-3'β), 95.4 (C-1β), 88.8 (C-1α), 78.9 (C-2β), 76.4 (C-2α), 76.2 (C-5β), 71.9 (C-5α), 66.4 (C-4β), 66.0 (C-4α), 61.4 (C-6α), 61.3 (C-6β), 20.9, 20.8, 20.7, 20.6 (Me, Ac) ppm. HRMS: calcd. for $C_{14}H_{16}O_9$ $[M + H]^+$ 329.0867, found 329.0864; calcd. for $[M + Na]^+$ 351.0687, found 351.0690; calcd. for $[M + K]^+$ 367.0426, found 367.0417.

5-*O*-*tert*-Butyldimethylsilyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ulose (17)[10]: A solution of 5-*O*-TBDMS-1,2-*O*-isopropylidene-α-D-xylofuranose[10] (1.05 g, 3.47 mmol) in dry CH_2Cl_2 (6 mL) was added under argon to a mixture of PDC (0.96 g, 2.57 mmol) and Ac_2O (1.1 mL, 11.6 mmol) in dry CH_2Cl_2 (12 mL), under argon. The mixture was stirred under reflux for 1 h 30 min, cooled to room temp., and concentrated. Diethyl ether (3×50 mL) was added to the gummy residue, mixture was filtered over Florisil and concentrated to afford the title compound as a waxy white solid (0.872 g, 97%). ^{1}H NMR ($CDCl_3$): δ 6.14 (d, 1H, $J_{1,2}$ 4.6 Hz, H-1), 4.37 (br. d, 1H, H-4), 4.28 (d, 1 H, H-2), 3.91, 3.90, 3.88, 3.87 (dd, part A of ABX system, H-5a $J_{4,5a}$ = 1.8, $J_{5a,5b}$ = 10.9 Hz,), 3.84, 3.83, 3.81, 3.80 (dd, part B of ABX system, $J_{4,5b}$ 2.0 Hz, H-5b), 1.46 (s, 3H, Me, isopr.), 1.45 (s, 3H, Me, isopr.), 0.86 (s, 9H, *t*-Bu, TBDMS), 0.06 (s, 3H, Me, TBDMS), 0.03 (s, 3H, Me, TBDMS); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.2 (*C*O), 114.2 (Cq, isop), 103.9 (C-1), 81.9 (C-4), 77.2 (C-2), 64.0 (C-5), 27.8 (Me), 27.3 (Me), 25.9 (3×Me, *t*-Bu), 18.3 (Cq, *t*-Bu), -5.4 (Me, TBDMS), -5.6 (Me, TBDMS).

5-*O*-*tert*-Butyldimethylsilyl-3-deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (18a) and 5-*O*-*tert*-butyldimethylsilyl-3-deoxy-3-*C*-[(*E*)-(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (18b): [(Ethoxycarbonyl)methylene]triphenylphosphorane (1.63 g, 4.67 mmol) was added to a solution of 3-ulose (**17**) (0.83 g, 2.7 mmol) in dry $CHCl_3$ (22 mL) and the mixture was stirred under reflux for 2 h. After concentration, the residue was chromatographed (EtOAc/cyclohexane, 1:9) as eluent to afford the (*Z*)-adduct **11** and its (*E*)-isomer **12** as colorless oils [0.806 g (81%) and 0.084 g (8%), respectively]. Spectral data were in full agreement with those reported.[11]

3-*C*-(Carboxymethylene)-3-deoxy-D-*erythro*-pentopyranose-3',2-lactone (20): 5-*O*-TBDMS-3-deoxy-3-C-[(*Z*)-(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (**11**, 0.11g, 0.29 mmol) was treated under reflux with Amberlite IR-120 H^+ resin as described for preparation of **4**. After filtration and concentration, the crude product was chromatographed (EtOAc/petroleum ether, 4:1) to afford the title compound (39 mg, 79%, anomeric mixture) as a white solid. R_f = 0.32 (EtOAc/petroleum ether, 4:1). m.p. 143-147 ºC (diethyl ether). ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.56 (d, OH-1β, J = 6.6 Hz,), 6.99 (d, OH-1α, J = 4.6 Hz), 5.99 (d, OH-4β, J = 5.1 Hz), 5.94-5.89 (m, H-3'β, OH-4α), 5.88 (br. s, H-3'α), 5.44 (t, H-1α), 4.96 (d, H-2α, $J_{1,2\ (\alpha)}$ = 3.5 Hz), 4.63 (d, H-2β, $J_{1,2\ (\beta)}$ = 6.8 Hz), 4.56-4.55 (m, H-4α, H-4β), 4.27 (t, H-1β), 4.05 (dd, , H-5aβ, $J_{4,5a(\beta)}$ = 8.1 Hz, $J_{5a,5b(\beta)}$ = 10.2 Hz), 3.75 (dd, H-5aα, $J_{4,5a(\alpha)}$ = 8.1 Hz, $J_{5a,5b(\alpha)}$ = 9.4 Hz), 3.42 (t, H-5bα, $J_{4,5b\ (\alpha)}$ = 10.1 Hz), 3.02 (t, H-5bβ) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, major anomer): δ = 172.8 (*C*O), 170.4 (C-3), 111.1 (C-3'), 90.3 (C-1), 78.4 (C-2), 65.5 (C-4), 62.6 (C-5) ppm. HRMS: calcd. for $C_7H_8O_5$ [M + H]$^+$ 173.0445, found 173.0443.

Experimental Procedures and Characterization of Compounds 10, 11, 12, 14a, 14b, 15 and 19

3-*C*-(Carboxymethylene)-3-deoxy-D-*ribo*-hexopyranose-3',4-lactone (10) and 1,2,6-Tri-*O*-acetyl-3-*C*-(carboxymethylene)-3-deoxy-D-*ribo*-hexopyranose-3',4-lactone (11): To a solution of 3-deoxy-3-*C*-[(*E*)-(ethoxycarbonyl)methylene]-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**2a**, 0.11g, 0.33 mmol) in MeOH (1.8 mL) was added Amberlite IR-120 H^+ resin (35 mg). The mixture was moderately stirred under

reflux overnight. After filtration of the resin and evaporation of the solvent, the crude was purified by CC (column chromatography) using AcOEt as eluent to afford **10** as a white solid. Ac_2O (1 mL) and py (2 mL) were then added to compound **10** and the mixture was stirred for 5 min. After co-evaporation with toluene (3×), the crude product was purified by CC (EtOAc/petroleum ether, 7:3) to afford **11** (67 mg, 63%, 2 steps) as a colorless oil.

Data for 10: R_f = 0.21 (EtOAc). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.36 (d, OH-1β, J = 6.3 Hz), 6.94 (d, OH-1α, *J* = 4.6 Hz), 6.15 (d, OH-2β, *J* = 5.3 Hz), 5.95−5.91 (m, H-3'α, H-3'β), 5.63 (d, OH−2α, J = 7.8), 5.24 (t, H−1α), 5.06 (t, OH-6), 4.99 (t, OH-6), 4.84 (d, H-4, $J_{4,5}$ = 9.4 Hz), 4.82 (d, H-4, $J_{4,5}$ = 9.9 Hz), 4.45 (ddd, H-2α), 4.33 (t, H-1β), 4.14 (ddd, H-2β), 3.73−3.49 (m, H-6aα, H-6aβ, H-6bα, H-6bβ, H-5), 3.13 (ddd, H-5) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 173.1 (*C*O), 172.4 (C-3α, C-3β), 112.1, 111.5 (C-3'α, C-3'β), 100.1 (C-1β), 93.5 (C-1α), 78.5 (C-5), 76.7 (C-4α, C-4β), 73.8 (C-5), 71.8 (C-2β), 69.4 (C-2α), 61.0 (C-6α, C-6β) ppm.

Data for 11: R_f = 0.31 (EtOAc/petroleum ether, 7:3). $[\alpha]_D^{20}$ = − 53 (c = 1.0, in CH_2Cl_2). IR (neat): 1777 cm^{-1} (C=O, lactone). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.51 (d, H-1α, $J_{1,2(\alpha)}$ = 4.3 Hz), 6.08 (t, H-3'α, $J_{2,3'(\alpha)} = J_{3',4(\alpha)}$ = 1.8), 6.01 (t, H-3'β, $J_{2,3'(\beta)} = J_{,3',4(\beta)}$ = 1.8 Hz), 5.83 (dd, H-2α), 5.73, 5.71 (d, part A of ABX system, H-2β, $J_{1,2(\beta)}$ = 7.6 Hz), 5.62, 5.60 (d, part B of ABX system, H-1β), 4.91 (m, H-4α, H-4β, $J_{4,5(\alpha)} = J_{4,5(\beta)}$ = 9.4 Hz), 4.50−4.44 (m, H-6aα, H-6aβ) 4.37−4.29 (m, H-6bα, H-6bβ, $J_{6a,6b(\alpha)} = J_{6a,6b(\beta)}$ = 12.4, $J_{5,6b(\alpha)} = J_{5,6b(\beta)}$ = 2.5 Hz), 3.88 (ddd, H-5α), 3.58 (ddd, H-5β), 2.21, 2.17, 2.16, 2.13, 2.12 (5s, Me, Ac, α, β) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0, 170.6, (*C*O, Ac), 170.4 (*C*O, lact., α, *C*O, lact., β) 169.2, 169.0, 168.8, 168.6 (*C*O, Ac, α, β), 163.8, 161.9 (C-3β, C-3α), 115.2 (C-3'β) 115.0 (C-3'α), 94.0 (C-1β), 89.4 (C-1α), 76.4 (C-5β), 76.0 (C-4α, C-4β), 74.0 (C-5α) 69.5 (C-2β), 67.9 (C-2α), 62.5, 62.5 (C-6α, C-6β), 20.8, 20.7, 20.5, 20.4 (Me, Ac) ppm. HRMS: calcd. for $C_7H_8O_5$ $[M + Na]^+$ 351.0670, found 351.0687; $C_7H_8O_5$ $[M + K]^+$ 367.0417, found 367.0426.

3-Deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-5,6-di-*O*-pivaloyl-D-*ribo*-hexofuranose (12): A solution of 3-deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-5,6-di-*O*-pivaloyl-α-D-*ribo*-hexofuranose (**5**, 55 mg, 0.12 mmol) in aq. AcOH (70%, 0.7 mL) was stirred under reflux for 5 h. The solvent was coevaporated with toluene (3×) and the crude product was purified by CC

(EtOAc/petroleum ether, 1:4) to afford **12** (31 mg, 62 %) as a colorless oil. R_f = 0.25 (EtOAc/petroleum ether, 1:4). $[\alpha]_D^{20}$ = +23 (c = 0.8, in CH_2Cl_2). IR (neat): 3571 cm^{-1} (OH), 1728 cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.12 (d, H-3'β), 6.04 (brs, H-3'α), 5.57-5.52 (m, H-1α, H-1β), 5.21 (ddd, H-5α, $J_{5,6a(\alpha)}$ = 2.5, $J_{5,6b(\alpha)}$ = 5.6 Hz), 5.09 (ddd, H-5β, $J_{4,5(\beta)}$ = 8.8, $J_{5,6a(\beta)}$ = 3.3, $J_{5,6b(\beta)}$ = 5.6) 4.98 (br. dd, H-2β), 4.94 (br. s, H-2α), 4.92−4.88 (m, H-4β), 4.85 (dt, H-4α, $J_{4,5(\alpha)}$ = 8.3 Hz), 4.54, 4.51 (part A of ABX system, H-6aα, $J_{6a,6b(\alpha)}$ = 12.4), 4.40−4.30 (m, OH-2α, H-6aβ, $J_{6a,6b\ (\beta)}$ = 12.1 Hz), 4.28-4.17 (m, H-6bα, H-6bβ, CH_2CH_3 α, CH_2CH_3 β), 3.97 (brs, OH-1β), 3.88 (brs, OH-1α), 1,31 (t, CH_2CH_3 α, J = 7.1 Hz), 1.30 (t, CH_2CH_3 β, J = 7.1 Hz), 1.24 (s, Me, piv, α, Me, Piv, β), 1.19 (s, Me, Piv, α), 1.18 (s, Me, Piv, β) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4 (*C*O, Piv, α), 178.1 (*C*O, Piv, β), 177.6 (*C*O, Piv, β), 177.3 (*C*O, Piv, α), 167.7 167.0 (*C*O, α, *C*O, β), 161.5 (C-3α), 161.1 (C-3β), 117.2 (C-3'α), 116.9 (C-3'β), 103.7 (C-1α), 96.9 (C-1β), 79.2 (C-4α), 77.9 (C-4β), 76.8 (C-2α), 73.1 (C-5α), 72.6, 72.5 (C-5β, C-2β), 62.7 (C-6α), 62.0, 61.9 (C-6β, CH_2CH_3 β), 61.4 (CH_2CH_3 α), 39.0, 38.9 (Cq, Piv, α, Cq, Piv, β), 27.3 (Me, Piv), 27.2 (Me, Piv), 14.2 (CH_2CH_3, α), 14.1 (CH_2CH_3, β) ppm.

3-Deoxy-3-*C*-[(*E*)-(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-5-*O*-pivaloyl-α-D-*erythro*-pentofuranose (14a) and 3-Deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)-methylene]-1,2-*O*-isopropylidene-5-*O*-pivaloyl-α-D-*erythro*-pentofuranose (14b): To a solution of 1,2-*O*-isopropylidene-5-*O*-pivaloyl-α-D-xylofuranos-3-ulose (**13**, 0.17 g, 0.63 mmol) in dry $CHCl_3$ (5 mL) was added [(ethoxycarbonyl)-methylene]triphenylphosphorane (0.37 g, 1.06 mmol). The mixture was stirred under reflux for 1 h 15 min. After evaporation of the solvent, the residue was purified by chromatography on silica-gel with EtOAc/cyclohexane (1:9) as eluent to afford (*E*)-**14a** (0.025 g, 12%) and its (*Z*)-isomer (**14b**, 0.15 g, 70%) as colorless oils.

Data for 14a: R_f = 0.29 (EtOAc/cyclohexane, 1:9). $[\alpha]_D^{20}$ = +160 (c = 1.2, in CH_2Cl_2). IR (neat): 1728 cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.18 (br. d, 1H, H-3'), 5.94 (d, 1H, H-1, $J_{1,2}$ = 4.6 Hz), 5.76 (br. s, 1H, H-4), 5.11 (br. d, 1H, H-2), 4.43, 4.42, 4.403, 4.39 (dd, part A of ABX system, 1H, H-5a, $J_{4,5a}$ = 2.0, $J_{5a,5b}$ = 11.6), 4.22−4.16 (m, 3H, H-5b, CH_2CH$_3$), 1.44 (s, 3H, Me, isopr.), 1.42 (s, 3H, Me, isopr.), 1,31 (t, 3H, CH_2CH_3, J = 7.1 Hz), 1.19 (s, 9H, Me, Piv) ppm. ^{13}C NMR (100 MHz $CDCl_3$): δ = 178.0 (*C*O, Piv), 165.3 (*C*O), 158.3 (C-3), 118.0 (C-3'), 113.7 (Cq, isopr.), 104.4 (C-1),

81.9 (C-2), 79.3 (C-4), 66.7 (C-5), 61.0 (CH_2CH_3), 38.7 (Cq, Piv), 28.1 (Me, isopr.), 27.8 (Me, isopr.), 27.4 (Me, Piv), 14.3 (CH_2CH_3) ppm.

Data for 14b: R_f = 0.18 (EtOAc/cyclohexane, 1:9). $[\alpha]_D^{20}$ = +143 (c = 1.0, in CH_2Cl_2). IR (neat): 1725 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.93 (br. d, 1H, H-3'), 5.93 (d, 1H, H-1), 5.72 (br. d, 1H, H-2, $J_{1,2}$ = 3.8), 5.05 (br. s, 1H, H-4), 4.32−4.21 (m, 4H, H-5a, H-5b, CH_2CH_3, $J_{4,5a}$ = 4.0 Hz), 1.50 (s, 3H, Me, isopr.), 1.43 (s, 3H, Me, isopr.), 1,31 (t, 3H, CH_2CH_3, J = 7.1 Hz), 1.19 (s, 9H, Me, Piv) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.0 (*C*O, Piv), 164.6 (*C*O), 154.8 (C-3), 117.2 (C-3'), 113.0 (Cq, isopr.), 105.2 (C-1), 78.3 (C-4), 78.2 (C-2), 64.7 (C-5), 60.8 (CH_2CH_3), 38.8 (Cq, Piv), 27.5 (Me, isopr.), 27.2 (Me, isopr.), 27.1 (Me, Piv), 14.3 (CH_2CH_3) ppm. Anal. Cald for $C_{17}H_{26}O_7$ (342.38): C, 59.64; H, 7.65. Found: C, 59.17; H, 8.01.

3-Deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-5-*O*-pivaloyl-α-D-*erythro*-pentofuranose (15): A solution of 3-deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-5-*O*-pivaloyl-α-D-*erythro*-pentofuranose (**14b**, 0.074 g, 0.22 mmol) in aq. AcOH (70%, 1.2 mL) was stirred under reflux for 2 h 15 min. The solvent was co-evaporated with toluene (3×) and the crude product was purified by CC (EtOAc/petroleum ether, 2:3) to afford **15** (0.046 g, 70 %) as a colorless oil. R_f = 0.35 (EtOAc/ petroleum ether, 2:3); $[\alpha]_D^{20}$ = +90 (c = 1.3, in CH_2Cl_2). IR (neat): 3525 cm^{-1} (OH), 1724 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.04-5.99 (m, 1H, H-3'α), 5.98 (brs, H-3'β), 5.62−5.57 (brd, H-1β), 5.50 (brs, 1H, H-1α), 5.05-4.92 (m, H-2α, H-4α, H-2β, H-4β), 4.43 (dd, H-5aα, $J_{4,5a(\alpha)}$ = 6.8, $J_{5a,5b(\alpha)}$ = 11.6 Hz), 4.29−4.21 (m, CH_2CH_3 α, CH_2CH_3 β, H-5aβ, H-5bβ), 4.18−4.11 (m, H-5bα, OH-2α), 4.01 (brs, OH-1α), 3.77 (brs, OH-1β), 1,32 (t, CH_2CH_3 α, CH_2CH_3 β, J = 7.1 Hz), 1.22 (s, 9H, Me, Piv, α), 1.19 (s, Me, Piv, β) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.6, 178.2 (*C*O, Piv, α, *C*O, Piv, β), 167.8, 166.8 (*C*O, α, *C*O, β), 161.6, 161.1 (C-3α, C-3β), 116.8 (C-3'β), 115.9 (C-3'α), 103.3 (C-1α), 96.8 (C-1β), 79.8, 77.7, 76.6, 72.9 (C-4α, C-4β, C-2α, C-2β), 66.9, 65.0 (C-5α, C-5β), 61.8, 61.5 (CH_2CH_3), 39.0, 38.9 (Cq, Piv,α, Cq, Piv, β), 27.2 (Me, Piv), 14.3, 14.2 (CH_2CH_3).

3-Deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (19): A solution of 5-O-TBDMS-3-deoxy-3-C-[(*Z*)-(ethoxycarbonyl)-methylene]-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose (**18b**, 0.28 g, 0.75 mmol)

in aq. AcOH (70%, 3.4 mL) was stirred at 70 ºC for 2 h 30 min. The solvent was co-evaporated with toluene (3×) and the residue was purified by CC (EtOAc/cyclohexane, 3:2) to afford **19** (0.16 g, 85 %) as a colorless oil. R_f = 0.27 (EtOAc/cyclohexane, 3:2). $[\alpha]_D^{20}$ = +216 (c = 1.2, in CH_2Cl_2). IR (neat): 3571 cm^{-1} (OH), 1722 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.98-5.90 (m, 2H, H-1, H-3'), 5.75 (brs, 1H, H-2), 4.91 (brs, 1H, H-4), 4.24 (q, 2H, CH_2CH_3, J = 7.1 Hz), 3.94, 3.91 (d, part A of ABX system, 1H, H-5a, $J_{4,5a}$ = 2.0, $J_{5a,5b}$ = 12.1 Hz), 3.75, 3.72 (d, part B of ABX system, 1H, H-5b, $J_{4,5b}$ = 3.5 Hz), 1.51 (s, 3H, Me, isopr.), 1.43 (s, 3H, Me, isopr.), 1,31 (t, 3H, CH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.9 (*C*O), 154.7 (C-3), 116.9 (C-3'), 113.0 (Cq, isop), 105.0 (C-1), 80.5 (C-4), 78.5 (C-2), 63.1 (C-5), 60.9 (CH_2CH_3), 27.4 (Me), 27.2 (Me), 14.3 (CH_2CH_3).

2.1.2. Furanose C-C-Linked Butenolides, Pyranose-Fused Butenolides and Biological Evaluation

The following section includes the paper:

"Synthesis and Biological Evaluation of Sugars Containing α,β-Unsaturated γ-Lactones", Xavier, N. M.; Silva, S.; Madeira, P. J. A.; Florêncio, M. H.; Silva, F. V. M.; Justino, J.; Thiem, J.; Rauter, A. P *Eur. J. Org. Chem.* **2008**, *2008*, 6134–6143.

and shows the synthetic work on furanose C-C-linked butenolides and pentopyranose- or hexopyranose-fused butenolides. The bioactivity of some of the new molecules is reported.

The role of the co-autors (besides the supervisors Rauter, A. P. and Thiem, J.) is specified as follows:

- Silva, S. made a contribution on the synthesis of the 5-keto sugar precursors;

- Madeira, P. J. A. and Florêncio, M. H. were responsible for the HRMS analysis;

- Silva, F. V. M. and Justino, J. carried out the biological tests.

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Synthesis and Biological Evaluation of Sugars Containing α,β-Unsaturated γ-Lactones

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Keywords: Wittig reaction / Lactones / Carbohydrates

Abstract

The stereocontrolled synthesis of new sugar derivatives carrying the α,β-unsaturated-δ-lactone (butenolide) moiety is described. Sugar-fused or sugar-linked butenolides can be constructed by an efficient reaction sequence involving Wittig olefination of 3- or 5-keto sugars, and intramolecular cyclization of the intermediate γ-hydroxy-α,β-unsaturated esters. The antimicrobial activities of the products and that of a known sugar-derived pyranoid α,β-unsaturated-δ-lactone were investigated against six pathogenic bacteria and six fungi. The pyranoid α,β-unsaturated δ-lactone **29** proved to be the most active compound in this series towards the plant pathogenic fungi *Colletotrichum coffeanum* (coffee berry disease) and *Pyricularia oryzae* (rice blast disease).

Introduction

α,β-Unsaturated-γ-lactones are abundant in both naturally occurring and synthetic products and are known to show a variety of antimicrobial [1] or cytotoxic [2] properties. Some of these compounds were reported to be potential antitumor agents [3], cyclooxygenase or phospholipase A2 inhibitors [4], or antibiotics [5].

In particular sugars bearing this moiety have become important molecular targets with respect to their significant biological profile and their functionalized nature, which make them suitable intermediates of distinct synthetic versatility [6].

The practice of incorporating unsaturated lactones into carbohydrates has been achieved with success in our laboratory. Some of these compounds (exocyclic unsaturated γ-lactones, compounds of type **A**, Figure 1) showed significant antifungal activity and are particularly effective against *Puccinia recondita* (wheat), *Botrytis cinerea* (pepper) and *Plasmopara viticola* (gravepine). They are considered potential wheat-, pepper-, or wine-protective agents [7]. Moreover, sugar-linked butenolides (endocyclic unsaturated γ-lactones, compounds of type **B**, Figure 1) have demonstrated their efficacy as potent and selective insecticides against *Drosophila melanogaster* Meig (fruitfly), and proved to be much more active than imidacloprid, the insecticide that is commercially used [8]. The fungicidal lactones were synthesized via Reformatsky-type reaction with a dialdofuranose as starting material [7, 9]. The approach described for the synthesis of the insecticidal compounds relied on the reaction of sugar epoxides with the dianion of phenylselenoacetic and -propionic acids, or their thioanalogues, followed by oxidation and elimination [7, 10]. Various routes leading to sugar C-linked butenolides have also been reported, including Wittig and iodo-lactonization reactions starting from a dialdofuranose and recently, ring-closing metathesis via sugar-derived Baylis-Hillman adducts [11, 12].

With respect to sugar-fused α,β-unsaturated γ-lactones, some literature reports describe their use for the preparation of bioactive natural products and branched-chain sugars [13,14].

We have recently demonstrated an effective route to access various butenolides fused to pento- and hexopyranoses [15]. The strategy is based on the Wittig olefination of furanos-3-uloses containing acid-labile 5-*O*- or 5,6-di-*O*- protecting groups, followed by acid hydrolysis. According to our previous findings and as part of our ongoing search for strategies to insert these structural motifs into carbohydrate templates for the design of new potentially biologically active substances, we have planned the synthesis of analogues of the described insecticidal butenolides (compounds type **B**, Figure 1).

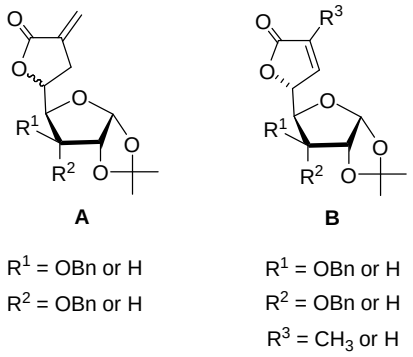


Figure 1. Structure of sugar-linked α,β-unsaturated-γ-lactones possessing fungicidal (**A**) and insecticidal (**B**) properties.

The developed methodology makes use of the Wittig reaction of 5-keto sugars with a resonance stabilized ylide to give α,β-unsaturated esters. The latter are spontaneously converted into the corresponding lactones in the presence of a γ-hydroxyl group, by controlling the stereochemistry of the Wittig products. Derivatives which differ in the steric bulk of the substituent at C-3 or in the C-3 configuration were synthesized in order to investigate the influence of these structural factors on the stereoselectivity. Moreover, to broaden the structural diversity of these sugar derivatives, we explored our recently reported methodology for the synthesis of new butenolides fused to pento- and hexopyranoses. One of the prospective applications of these bicyclolactones is the synthesis of fused-disaccharides by diol addition.

The results of the antimicrobial activity evaluation performed on the newly synthesized sugar-C-C-linked butenolides as well as on the previously reported bicyclic fused derivatives are presented here. To extend the range of the sugar-based unsaturated lactones tested, a pyranoid α,β-unsaturated γ-lactone [16] was included in our set of

compounds. In addition, we compared these results with related data for known antifungal α-methylene-γ-butyrolactones in order to rationalize, in terms of structure, the influence of the lactone system on the observed bioactivities. For this purpose we especially want to emphasize a possible relationship between the Michael-accepting ability of the tested compounds and their biological activities.

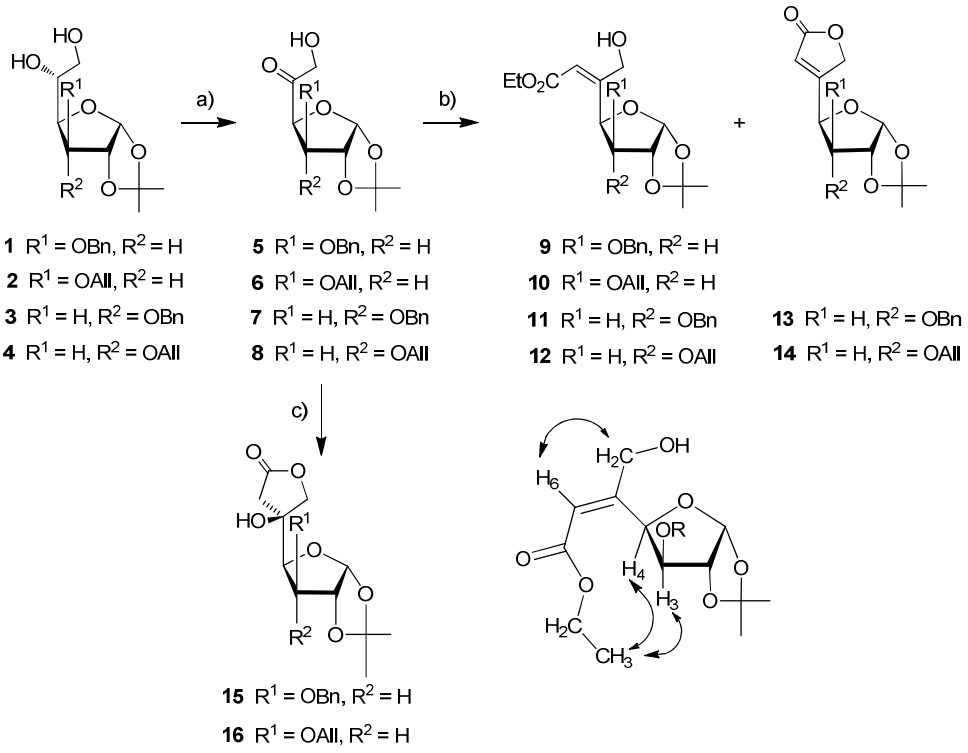
Results and Discussion

1. Chemistry

1.1. Sugar-C-C-Linked Butenolides

The synthesis of 5-keto sugars **5–8** (Scheme 1) was achieved by regioselective oxidation of the secondary hydroxyl group of the 5,6-diol precursors **1**–**4** with the system Bu_2SnO/NBS [17] in 90, 78, 60 and 61% yield, respectively. The ^{1}H-NMR spectra of the α-hydroxy ketone products show AB-system patterns for H-6a, H-6b, with geminal coupling constants from 20.2 to 20.5 Hz. The carbonyl groups of **5**-**8** give rise to characteristic signals in the ^{13}C-NMR spectra (δ = 208.2, 208.2, 207.1 and 207.3 ppm, respectively) and show IR band absorptions at 1725 and 1730 cm^{-1}. The lower yield obtained for the *ribo* derivatives may result from dimerization of the α-hydroxy ketones, which must depend on the stereochemistry at C-3, as suggested in the literature [17]. Hence dimerization occurs to a larger extent in *ribo* than in *xylo* compounds in which the orientation of the C-3 substituent results on increased steric hindrance to the formation of dimers. The 5-keto substrates were subjected to Wittig reaction with [(ethoxycarbonyl)methylene]triphenylphosphorane in refluxing chloroform to give compounds **9**–**12**. Starting from 3-*O*-benzyl- and 3-*O*-allyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**5**, **6**), the (*Z*)-α,β-unsaturated esters **9**, **10** were obtained in 74% and 60 % yield, respectively, and no cyclization was observed. In the ^{1}H NMR spectra, the signals of the olefinic protons appear at δ 6.02 and δ 6.08 ppm, respectively, as broad singlets. Diagnostic signals for the configuration assignment of these molecules are the H-4 protons, which are relatively downfield shifted (δ = 5.83 and δ = 5.84 ppm), thus reflecting the orientation of the ethoxycarbonyl group. Furthermore, the (*Z*)- configuration around the double bond could be confirmed by NOESY experiments, due to the correlations of H-3and H-4 with CH_3 (Et) protons and those of H-6 with H-

5'a, H-5'b. However, when the *ribo*-hexofuranos-5-ulose derivatives **7**–**8** were used as starting materials, the corresponding Wittig reaction provided mainly the formation of the (*E*)-adducts, the spontaneous cyclization of which gave the α,β-unsaturated-γ-lactones **13, 14** in 47% and 49% yield, respectively. The carbonyl groups of the butenolide moeties were confirmed by the signals at δ = 173.3 ppm in their ^{13}C NMR spectra. In the ^{1}H NMR spectra, olefinic protons give rise to signals at δ = 6.06 and δ = 6.12 ppm, respectively, and as a consequence of lactonization, chemical shifts values for H-4 around δ = 4.85 ppm are much smaller than those observed for their acyclic (*Z*)-aducts **11** and **12**, which were isolated in only 12% and 11% yield, respectively. These results suggest that the stereoselectivity of the Wittig reaction to the formation of the (*E*)-isomers and consequently, to their spontaneous lactonization, depends on the orientation of the C-3 substituent. A possible steric hindrance due to C-3 configuration in *xylo*-hexofuranose derivatives with a bulky benzyloxy group or with allyl ether protection at position 3 may be envisaged. The 5-keto sugars **5**, **6** were also used as precursors for a Reformatsky reaction with ethyl bromoacetate to afford the sugar-linked β-hydroxy lactones **15, 16**, formed in low yield (16 and 19 %, respectively), together with a complex mixture of degradation products. A salient feature of the ^{1}H NMR spectra of **15** and **16** is the two separate sets of AB systems for the five-membered ring lactone unit, assigned for H-5'a, H-5'b, and H-6a, H-6b, the latter shifted upfield. The presence of the signals at δ = 174.8 and δ = 175.1 ppm for the carbonyl groups of **15** and **16**, respectively, in their ^{13}C NMR spectra confirmed the lactone skeleton. Our proposed configuration for the stereogenic centre (C-5) of the formed lactone is based on the assumption that the nucleophilic attack of the Reformatsky reagent to **5-6** should occur from the less hindered face of the carbonyl group.

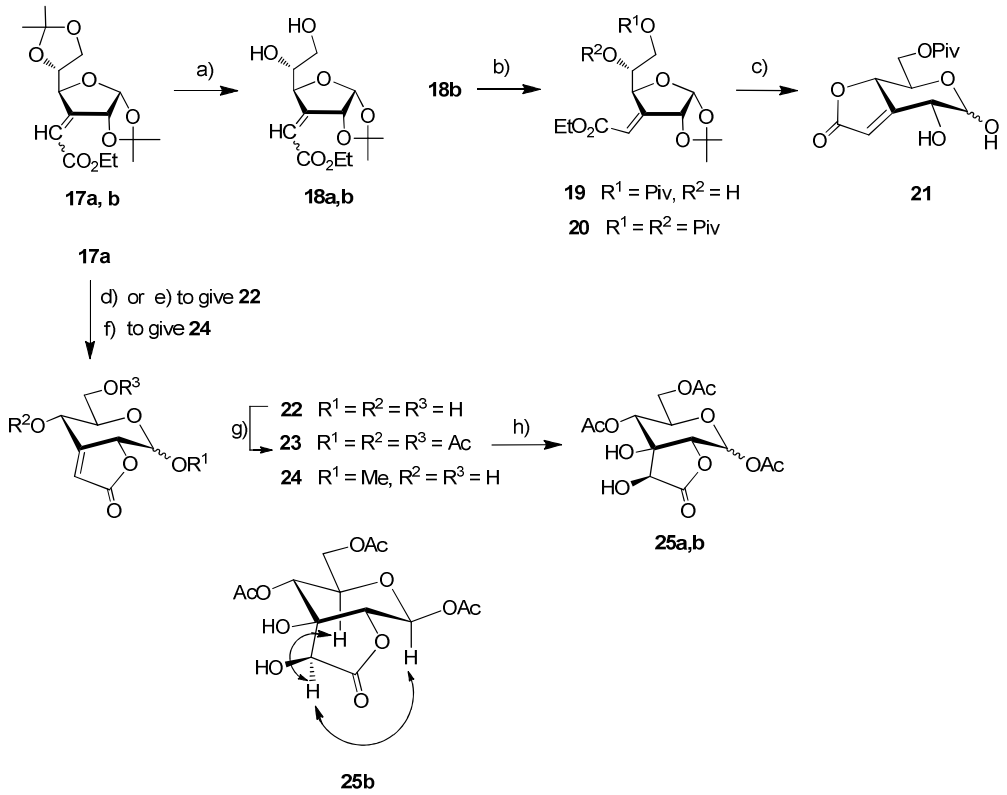


Scheme 1. Reactions and conditions: a) Bu_2SnO, toluene, reflux overnight, then NBS, CH_2Cl_2, 5 min; b) $Ph_3P{=}CHCO_2Et$, $CHCl_3$, reflux; c) $BrCH_2CO_2Et$, Zn, THF, 50 °C.

1.2. Sugar-Fused Butenolides

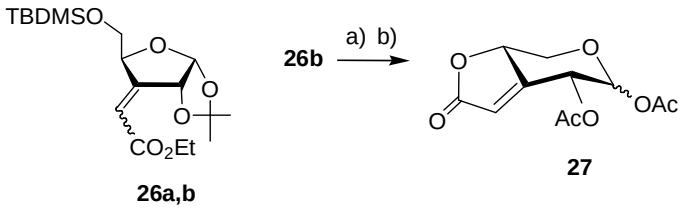
The synthesis of sugar-fused butenolides was accomplished following the approach previously reported by us, starting from readily available furanos-3-uloses [15]. Thus, Wittig reaction of 1,2;5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranosid-3-ulose [9] with [(ethoxycarbonyl)methylene]triphenylphosphorane in refluxing chloroform afforded the known (*E*)- and (*Z*)-α,β-unsaturated esters **17a**,**b** [18] (Scheme 2) in 12% yield and 68% yield, respectively. The (*E*)-adduct **17b** was partially hydrolysed at the primary acetonide with aq. acetic acid (60%) to the corresponding diol **18b** which was subsequently treated with pivaloyl chloride in py/CH_2Cl_2 at 0 °C. The mono-pivaloyl derivative **19**, selectively obtained in 81% yield, was submitted to hydrolysis with aq. acetic acid (70%) under reflux to provide the hexopyranose-fused butenolide **21** as a mixture of α,β-anomers in 58% yield. Noteworthy in this step, in which cleavage of the acetal, isomerization to the pyranose form, and accompanying intramolecular lactonization occur, is that the pivaloyl group unexpectedly remains in the final product and no migration was observed. This feature could indeed be confirmed by the observed

HMBC correlation between H-6a,b and the carbonyl carbon of the pivaloyl group. On the other hand, conversion of the (*Z*)-α,β-unsaturated ester **17a** to the butenolide **22** in one single step was initially performed by treatment with IR-120 H^+ resin in refluxing methanol overnight in 90% yield. Manipulation of the reaction conditions using an ion-exchange resin with stronger acidic properties, Dowex-50W, the reaction time was reduced to 2 h, whereas the corresponding methyl glycoside **24** was formed in 57% yield after overnight stirring. Dihydroxylation of the triacetate-derived butenolide **23** with osmium tetroxide gave the α/β-*cis*-diols **25a,b** which could be separated by column chromatography and isolated in 33 and 23% yield, respectively. The (*S*)-configuration of the new stereocenter could be assigned by 2D-NOESY analysis of the β-anomer, with the detection of NOEs between H-3–H-5 and H-3–H-1 (Scheme 2). These compounds constitute non-natural fused disaccharides which comprise a butyrolactone and a pyranose system.



Scheme 2. Reactions and conditions: a) AcOH 60% aq., room temp.; b) PivCl, CH_2Cl_2/py, 0 ºC; c) AcOH 70% aq., reflux; d) Amberlite IR-120 H^+, MeOH, reflux overnight; e) DOWEX 50W H^+, MeOH, reflux, 2 h; f) DOWEX 50W H^+, MeOH, reflux, overnight; g) Ac_2O, py, room temp., 5 min; h) OsO_4, py, room temp.

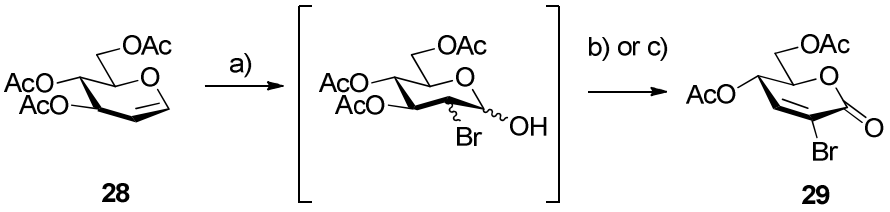
Similarly to the hexofuranose derivatives, the (*E*)-α,β-unsaturated ester **26b**, a minor stereoisomer, prepared by Wittig olefination of 1,2-*O*-isopropylidene-5-*O*-*tert*-butyldimethylsilyl-α-D-*erythro*-furanos-3-ulose [15], was subjected to an analogous acid hydrolysis, which was followed by acetylation (Scheme 3). The bicyclolactone **27**, the structure of which comprises the butenolide moiety fused to a pentopyranose unit at positions 3 and 4, was obtained in 74 % overall yield.



Scheme 3. Reactions and conditions: a) AcOH 70%, reflux; b) Ac_2O, py, room temp., 5 min.

1.3. Synthesis of a Sugar Pyranoid α,β-Unsaturated δ-Lactone

The hex-2-enono-1,5-lactone **29** was synthesized by reaction of 1,5-anhydro-3,4,6-tri-*O*-acetyl-2-deoxy-D-arabino-hex-1-enitol (**28**) (non-preferred trivial name: 3,4,6-tri-*O*-acetyl-D-glucal) with *N*-bromosuccinimide (NBS) and water followed by oxidation of the 2-bromolactol formed, according to the approach previously reported (Scheme 4) [16]. Two different chromium-based reagents were used at the oxidation step: pyridinium chlorochromate (PCC) as in the original procedure and pyridinium dichromate (PDC). In both cases, after reaction completion, the mixture was filtered through a short Florisil plug, which efficiently retained the green Cr^{III} species, facilitating the purification of the enonolactone **29** by column chromatography. However the first oxidizing methodology provided the best result in this one-pot, two-step procedure, forming the target compound in 43% overall yield, when compared to 31% yield using PDC.

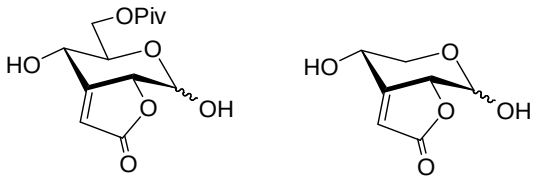


28 **29**

Scheme 4. Reactions and conditions: a) NBS, H_2O/THF; b) PCC, molecular sieves (3 Å), CH_2Cl_2, room temp.; c) PDC, Ac_2O, CH_2Cl_2, room temp.

2. Antibacterial and Antifungal Screening

The antimicrobial activities of sugar-linked butenolides **13**, **14**, sugar-fused butenolides **22**, **23, 30** [15] and **31** [15] (Figure 2) and pyranoid α,β-unsaturated δ-lactone **29** were investigated using the paper disk diffusion method [19, 20]. These compounds were evaluated for their in vitro antibacterial activity against pathogens such as *Bacillus cereus*, *Bacillus subtilis*, *Enterococcus faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus.* Their antifungal activity was studied on a panel of plant pathogenic fungi which may also cause human allergies including *Botrytis* spp., *Colletotrichum coffeanum*, *Fusarium culmorum*, *Pyricularia oryzae*, and *Rhizopus* spp., and the human fungal pathogen *Candida albicans*. The results are presented in Table 1.



30 **31**

Figure 2. Structure of sugar-fused butenolides **30**, **31** submitted to bioactivity tests.

Table 1. Antimicrobial activities of compounds **13**, **14**, **22**, **23**, **29**, **30** and **31** [a].

								Control [b]	
	13	**14**	**22**	**23**	**29**	**30**	**31**	I	II
Bacteria									
Bacillus cereus	<6.4	<6.4	<6.4	<6.4	11	<6.4	<6.4	24	38
Bacillus subtilis	<6.4	9	10	16	<6.4	10	<6.4	30	46
Enterococcus faecalis	<6.4	<6.4	<6.4	<6.4	9	<6.4	<6.4	26	40
Escherichia coli	<6.4	<6.4	<6.4	<6.4	9	<6.4	<6.4	28	42
Pseudomonas aeruginosa	<6.4	<6.4	<6.4	<6.4	9	<6.4	<6.4	<6.4	22
Staphylococcus aureus	<6.4	<6.4	<6.4	<6.4	9	<6.4	<6.4	27	40
Fungi									
Botrytis spp.	<6.4	<6.4	8	8	11	<6.4	<6.4	<6.4	20
Candida albicans	<6.4	9	8	8	10	8	8	<6.4	16
Colletotrichum coffeanum	<6.4	<6.4	<6.4	<6.4	16	<6.4	<6.4	16	24
Fusarium culmorum	<6.4	<6.4	<6.4	<6.4	<6.4	<6.4	<6.4	12	18
Pyricularia oryzae	<6.4	<6.4	<6.4	<6.4	15	<6.4	<6.4	39	63
Rhizopus spp.	<6.4	<6.4	<6.4	<6.4	<6.4	<6.4	<6.4	11	18

[a] Compounds' solutions tested [300 μg compound in DMSO (15 μL)]. [b] Chloramphenicol was used for all bacteria and for C. albicans, whereas actidione was used for the filamentous fungi; a solution of the control (I-30 μg; II -300 μg) in DMSO (15 μL) was used.

The sugar-linked butenolide **14** exhibited weak effects toward *Bacillus subtilis* and *Candida albicans* while the 3-*O*-benzyl counterpart **13**, showed virtually no activity at all. Regarding these results and in contrast with those of the analogues possessing an α-methylene-γ-lactone moiety (compounds type **B**, Figure 1), particularly against *Botrytis* spp., *Fusarium culmorum* and *Pyricularia oryzae*, it is clear that the exocylic double bond in the lactone enhances the antifungal activity of these compounds. Given their structure, the exocyclic α,β-unsaturated γ-lactones have greater ability than the endocyclic derivatives to act as Michael acceptors, which is commonly related to the bioactivity of α,β-unsaturated carbonyl compounds [21]. Hence, the presence of the

quaternary hindered β-carbon in the lactone system of **13** and **14**, considerably reduces their propensity to a nucleophilic attack, especially by sulfhydryl groups of enzymes.

Sugar-fused butenolides **22**, **23** and **30** displayed selective antibacterial activity against *Bacillus subtilis*; the highest activity was observed for the triacetate derivative **23** with moderate effect. The antibacterial effect of compound **31** is practically negligible. With respect to the antifungal activity assays, all the butenolide derivatives showed similar and weak activities toward *Candida albicans*. Compounds **22** and **23** exhibited weak activities against *Botrytis* spp., although butenolides **30** and **31** were inactive against these pathogens. The results of the antimicrobial evaluation made on this series may be also related to the presence of the hindered double bond in the lactone conjugated system, which is now fused to a six-membered ring, making the system less susceptible to Michael addition. The pyranoid α,β-unsaturated δ-lactone **29** proved to be the most active compound of this set; **29** is active against all the bacteria tested, except for *Bacillus subtilis*, for which no effect was detected. Regarding the tested fungi, lactone **29** shows weak activities against *Botrytis* spp and *Candida albicans* and moderate activity against *Colletotrichum coffeanum* (coffee berry disease) and *Pyricularia oryzae* (rice blast disease). The greater Michael-accepting ability of **29** when compared to that of the previous lactones, due to the electron withdrawing influence of the bromine atom and absence of steric hindrance in the reactive double bond, may indeed contribute to the biological results obtained.

Conclusions

A series of novel sugar-containing butenolides was synthesized. C-C-Linked sugar-butenolides were prepared by Wittig olefination of hexofuranos-5-uloses followed by intramolecular lactonization of the intermediate γ-hydroxy-α,β-unsaturated esters. The configuration at C-3 seems to be an important structural factor to control the cyclization step. Hence, butenolides were prepared from *ribo*-furanos-5-ulose derivatives, while olefination of *xylo*-5-uloses did not afford the appropriate stereoisomer for spontaneous cyclization. The synthesis of sugar-fused butenolides was accomplished starting from pento- and hexofuranos-3-uloses, using our previously reported Wittig olefination-acid hydrolysis approach [15]. The biological evaluation performed on some of the new targets, suggested that the presence of a non-hindered double bond in the conjugated

system is essential for the biological activity. The low molecular flexibility of the new sugar-linked and sugar-fused butenolides possessing a quaternary Cβ does not allow their expression as Michael acceptors and probably explains the weak antimicrobial effect observed for these compounds. The pyranoid α,β-unsaturated δ-lactone **29**, which is undoubtedly more susceptible to Michael addition, displays activity against most of the bacteria studied and moderate antifungal effect toward *Colletotrichum coffeanum* and *Pyricularia oryzae*, confirming therefore the above disclosed assumptions.

Experimental Section

1. Chemistry

General Methods: Melting points were determined with a Stuart Scientific SMP 3 apparatus or a Leitz apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 343 polarimeter at 20 ºC. IR spectra were acquired using a Hitachi 270-50. ^{1}H and ^{13}C NMR spectra were recorded with a BRUKER Avance 400 spectrometer or a Bruker AMX-400 spectrometer, both operating at 400.13 MHz for ^{1}H or 100.62 MHz for ^{13}C. Chemical shifts are expressed in parts per million and are referenced either to TMS as internal standart for ^{1}H or to the solvent signal (^{13}C NMR, δ = 77.16 for $CDCl_3$). Assignments were made, when needed, with the help of DEPT, COSY, HMQC, NOESY and HMBC experiments. HRMS spectra were acquired in an Apex Ultra FTICR Mass Spectrometer equipped with an Apollo II Dual ESI/MALDI ion source, from Bruker Daltonics, and a 7T actively shielded magnet from Magnex Scientific.

All reactions were followed by TLC on Merck 60 F254 silica gel aluminum plates. UV at 254 nm and a solution of 10% H_2SO_4 in EtOH were used for detection. Column chromatography (CC) was carried out on silica gel 60 G (0.040–0.063 mm, E. Merck).

General Procedure for the Synthesis of Hexofuranos-5-uloses 5–8: Dibutyltin oxide (0.221g, 0.89 mmol) was added to a solution of 5,6-diol (0.81 mmol) in toluene (5.4 mL). The mixture was stirred under reflux with a Dean-Stark aparatus. The solvent was evaporated and the residue was dried in vacuum for 30 min. The crude was then taken up in dry $CHCl_3$ (5.4 mL) and NBS (0.158g, 0.89 mmol) was added. The resulting

solution was stirred for 5 min. The solvent was removed in vacuum, and the residue was purified by column chromatography (CC) on silica gel.

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (5): 3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose [22] (**1**, 0.250 g, 0.81 mmol) gave **5** (0.220 g, 90 %) as a white solid, after purification by CC (EtOAc/ petroleum ether, 3:7). NMR spectroscopic data were in full agreement with those reported in the literature [17].

3-*O*-Allyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (6): 3-*O*-Allyl-1,2-*O*-isopropylidene-α-D-glucofuranose [23] (**2**, 0.374 g, 1.44 mmol) gave **6** (0.291 g, 78%) as a colorless oil, after purification by CC (EtOAc/cyclohexane, 3:7). R_f = 0.28 (EtOAc/petroleum ether, 1:9). $[\alpha]_D^{20}$ = –70 (c = 1, in CH_2Cl_2). IR (neat): 1725 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$): δ = 6.05 (d, 1H, H-1, $J_{1,2}$ = 3.5 Hz), 5.80−5.71 (m, 1H, C*H* allylic), 5.25–5.17 (m, 2H, =CH_2 allylic), 4.80 (d, 1H, H-4, $J_{3,4}$ = 3.5 Hz), 4.58 (d, 1H, H-2), 4.57, 4.56, 4.52, 4.51 (dd, part A of ABX system, 1H, H-6a, $J_{6a,6b}$ = 20.2, $J_{OH,H-6b}$ = 4.3 Hz), 4.49, 4.48, 4.44, 4.43 (dd, part B of ABX system, 1H, H-6b, $J_{OH,\ H-6b}$ = 4.0 Hz), 4.25 (d, 1H, H-3), 4.07, 4.06, 4.05, 4.03 (dd, part A of ABX system, 1H, H-a, OCH_2 allylic, $J_{a,b}$ = 12.6, $J_{a,H-all}$ = 5.3 Hz), 3.95, 3.94, 3.92, 3.91 (dd, part B of ABX system, 1H, H-b, OCH_2 allylic, $J_{b,H-all}$ = 5.8 Hz), 2.93 (t, 1H, OH), 1.48 (s, 3H, Me), 1.34 (s, 3H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.2 (*C*O), 133.3 (*C*H allylic), 118.2 (=*C*H_2 allylic), 112.7 (Cq, isopr.), 106.0 (C-1), 84.6 (C-4), 83.2 (C-3), 81.9 (C-2), 71.5 (O*C*H_2 allylic) 68.3 (C-6), 27.0 (Me), 26.3 (Me) ppm. HRMS: calcd. for $C_{12}H_{18}O_6$ $[M + H]^+$ 259.1176, found 259.1177; calcd. for $[M + Na]^+$ 281.0996, found 281.0996 ; calcd. for $[M + K]^+$ 297.0735, found 297.0735.

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranos-5-ulose (7): 3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-allofuranose [24] (**3**, 1.00 g, 3.22 mmol) gave **7** (0.595 g, 60%) as a colorless syrup after purification by CC (EtOAc/petroleum ether, 2:3). R_f = 0.36 (EtOAc/petroleum ether, 2:3). $[\alpha]_D^{20}$ = +24 (c = 0.4, in CH_2Cl_2). IR (neat): 1730 cm^{-1} (C=O). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7. 27 (m, 5H, Ph), 5.81 (d, 1H, H-1, $J_{1,2}$ = 3.4 Hz), 4.76, 4.73 (d, part A of AB system, 1H, H-a, OCH_2Ph, $J_{a,b}$ = 11.9 Hz), 4.64–4.59 (m, 2H, H-b, H-4), 4.57 (br. t, 1H, H-2), 4.45, 4.40, (d, part A of AB system, 1H, H-6a, $J_{6a,6b}$ = 20.2 Hz), 4.38, 4.33, (d, part B of AB system, 1H, H-6b), 3.81 (dd, 1H, H-

3, $J_{2,3}$ = 4.4, $J_{3,4}$ = 9.3 Hz), 1.59 (s, 3H, Me),1.36 (s, 3H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.1 (*C*O), 136.7 (Cq, Ph), 128.6, 128.3, 128.1 (*C*H, Ph), 113.8 (Cq, isopr.), 104.6 (C-1), 80.4 (C-4), 79.4 (C-3), 77.6 (C-2), 72.5 (O*C*H$_2$Ph), 66.5 (C-6), 26.9 (Me), 26.5 (Me) ppm. HRMS: calcd. for $C_{16}H_{20}O_6$ [*M* + H]$^+$ 309.1333, found 309.1335; calcd. for [*M* + Na]$^+$ 331.1152, found 331.1159; calcd. for [*M* + K]$^+$ 347.0891, found 347.0884.

3-*O*-Allyl-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranos-5-ulose (8): 3-*O*-Allyl-1,2-*O*-isopropylidene-α-D-allofuranose [25] (**4**, 0.473 g, 1.82 mmol) gave **8** (0.289 g, 61%) as a colorless oil after purification by CC (EtOAc/cyclohexane, 3:7). R_f = 0.23 (EtOAc/cyclohexane, 2:3). $[\alpha]_D^{20}$ = +56 (c = 0.7, in CH_2Cl_2). IR (neat): 1725 cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00−5.87 (m, 1H, C*H* allylic), 5.87 (d, 1H, H-1, $J_{1,2}$ = 3.6 Hz), 5.37-5.24 (m, 2H, =C*H*$_2$ allylic), 4.67 (br. t, 1H, H-2), 4.60 (d, 1H, H-4, $J_{3,4}$ = 9.1 Hz), 4.51, 4.46 (d, part A of AB system, 1H, H-6a, $J_{6a,6b}$ = 20.5 Hz), 4.46, 4.41 (d, part B of AB system, 1H, H-6b), 4.23, 4.22, 4.20, 4.19 (dd, part A of ABX system, 1H, H-a, OC*H*$_2$ allylic, $J_{a,b}$ = 12.6, $J_{a,H\text{-}all}$ = 5.8 Hz), 4.14, 4.13, 4.11, 4.10 (dd, part B of ABX system, 1H, H-b, OC*H*$_2$ allylic, $J_{b,H\text{-}all}$ = 5.8 Hz), 3.83 (dd, 1H, H-3, $J_{2,3}$ = 4.0 Hz), 3.09 (br. s, 1H, OH), 1.59 (s, 3H, Me), 1.38 (s, 3H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.3 (*C*O), 133.8 (*C*H allylic), 119.1 (=*C*H$_2$ allylic), 113.9 (Cq, isop), 104.6 (C-1), 80.3 (C-4), 79.8 (C-3), 77.8 (C-2), 72.0 (O*C*H$_2$ allylic), 66.7 (C-6), 26.9 (Me), 26.6 (Me) ppm. HRMS: calcd. for [*M* + Na]$^+$ 281.0996, found 281.0996.

General Procedure for the Preparation of the α,β-Unsaturated Esters 9–12 and Butenolides 13–14: [(Ethoxycarbonyl)methylene]triphenylphosphorane (0.153 g, 0.44 mmol) was added to a solution of hexofuranos-5-ulose (0.26 mmol) in dry $CHCl_3$ (2.1 mL). The mixture was stirred under reflux until complete conversion, as indicated by TLC. The solvent was removed and the residue was purified by column chromatography (CC) on silica gel.

Ethyl (5*Z*)-3-*O*-Benzyl-5,6-dideoxy-5-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-*xylo*-5-enoheptofuranuronate (9): Wittig olefination of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**5**, 0.080 g, 0.26 mmol) was completed within 4 h to give **9** (0.073 g, 75%) as a colorless syrup after purification by CC

(EtOAc/petroleum ether, 1:4). R_f = 0.47 (EtOAc/petroleum ether, 1:4). $[\alpha]_D^{20}$ = − 91 (c = 0.6, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32−7.21 (m, 5H, Ph), 6.02 (s, 1H, H-6), 6.00 (d, 1H, H-1, $J_{1,2}$ = 3.6 Hz), 5.83 (s, 1H, H-4), 4.65–4.59 (m, 2H, H-a, OC*H*$_2$Ph, H-2, $J_{a,b}$ = 11.6 Hz), 4.45-4.40 (m, 2H, H-b, OC*H*$_2$Ph, H-3), 4.35 (br. s, 2H, H-5'a, H-5'b), 4.08 (q, 2H, C*H*$_2$CH$_3$, *J* = 7.2 Hz), 1.52 (s, 3H, Me), 1.34 (s, 3H), 1,25 (t, 3H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0 (*C*O), 156 (C-5), 137.1 (Cq, Ph), 128.4, 128.0, 127.9, (*C*H, Ph), 117.0 (C-6), 112.1 (Cq, isopr.), 104.9 (C-1), 83.2 (C-3), 82.5 (C-2), 80.0 (C-4), 72,4 (O*C*H$_2$Ph), 64.5 (C-5'), 60.2 (*C*H$_2$CH$_3$), 26.9 (Me), 26.4 (Me), 14.2 (CH$_2$*C*H$_3$) ppm. HRMS: calcd. for $C_{20}H_{26}O_7$ [*M* + H]$^+$ 379.1751, found 379.1754; calcd. for [*M* + Na]$^+$ 401.1571, found 401.1574; calcd. for [*M* + K]$^+$ 417.1310, found 417.1314.

Ethyl (5*Z*)-3-*O*-Allyl-5,6-dideoxy-5-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-*xylo*-5-enoheptofuranuronate (10): Wittig olefination of 3-*O*-allyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**6**, 0.184 g, 0.71 mmol) was completed within 4 h and gave **10** (0.139 g, 60%) as a colorless syrup, after purification by CC (EtOAc/cyclohexane, 1:4). R_f = 0.28 (EtOAc/ petroleum ether, 1:4). $[\alpha]_D^{20}$ = –31 (c = 0.4, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.08 (br. s, 1H, H-6), 5.99 (d, 1H, H-1, $J_{1,2}$ = 3.8 Hz), 5.84 (s, 1H, H-4), 5.82–5.72 (m, 1H, *C*H allylic), 5.26-5.13 (m, 2H, =C*H*$_2$ allylic), 4.57 (d, 1H, H-2), 4.38 (d, 1H, H-3, $J_{3,4}$ = 3.3 Hz), 4.34 (br. d, 2H, H-5'a, H-5'b), 4.19 (q, 2H, C*H*$_2$CH$_3$, *J* = 7.1 Hz), 4.08, 4.06, 4.05, 4.03 (dd, part A of ABX system, 1H, H-a, OC*H*$_2$ allylic, $J_{a,b}$ = 12.9, $J_{a,H\text{-}all}$ = 5.3 Hz), 3.95, 3.94, 3.92, 3.91 (dd, part B of ABX system, 1H, H-b, OC*H*$_2$ allylic, $J_{b,H\text{-}all}$ = 5.8 Hz), 2.54 (t, 1H, OH, *J* = 5.8 Hz), 1.53 (s, 3H, Me), 1.34 (s, 3H, Me), 1,29 (t, 3H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9 (*C*O), 156.3 (C-5), 133.8 (*C*H allylic), 117.9 (=*C*H$_2$ allylic), 117.1 (C-6), 112.1 (Cq, isopr.), 105.0 (C-1), 83.6 (C-3), 82.9 (C-2), 79.9 (C-4), 71.5 (O*C*H$_2$ allylic) 64.5 (C-5'), 60.4 (*C*H$_2$CH$_3$), 27.0 (Me), 26.5 (Me), 14.4 (CH$_2$*C*H$_3$) ppm. HRMS: calcd. for $C_{16}H_{24}O_7$ [*M* + H]$^+$ 329.1595, found 329.1593; calcd. for [*M* + Na]$^+$ 351.1414, found 351.1410; calcd. for [*M* + K]$^+$ 367.1154, found 367.1152.

Ethyl (5*Z*)-3-*O*-Benzyl-5,6-dideoxy-5-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-*ribo*-5-enoheptofuranuronate (11) and 3-*O*-Benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-5-enoheptofuranurono-7,5'-lactone (13): Wittig olefination

of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranos-5-ulose (**7**, 0.187 g, 0.61 mmol) was completed within 1 h 30 min and gave **11** (0.027g, 12%) as a colorless syrup and **13** (0.096 g, 47%) as a white solid, after purification by CC (EtOAc/petroleum ether, 1:4).

Data for **11**: R_f = 0.45 (EtOAc/petroleum ether, 2:3). $[\alpha]_D^{20}$ = + 6 (c = 0.9, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.27 (m, 5H, Ph), 6.06 (s, 1H, H-6), 5.85 (d, 1H, H-4, $J_{3,4}$ = 9.9 Hz), 5.74 (d, 1H, H-1, $J_{1,2}$ = 3.3 Hz), 4.70, 4.66 (d, part A of AB system, 1H, H-a, OCH_2Ph, $J_{a,b}$ = 11.9 Hz), 4.58 (t, 1H, H-2), 4.56, 4.53 (d, part B of AB system, 1H, H-b, OCH_2Ph), 4.28–4.09 (m, 3H, H-5'a, CH_2CH_3), 4.03, 4.01, 3.99, 3.97 (dd, part B of AB system, 1H, H-5'b, $J_{5a,5b}$= 14.9, $J_{5b,\ OH}$ = 7.1 Hz), 3.81 (dd, 1H, H-3, $J_{2,3}$ = 3.8 Hz), 1.65 (s, 3H, Me), 1.37 (s, 3H, Me), 1,26 (t, 3H, CH_2CH_3, J = 7.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9 (*C*O), 152.2 (C-5), 137.6 (Cq, Ph), 128.5, 128.1, 128.0 (*C*H, Ph), 120.0 (C-6), 113.6 (Cq, isopr.), 104.2 (C-1), 81.0 (C-3), 77.8 (C-2), 75.0 (C-4), 72,3 (OCH_2Ph), 62.5 (C-5'), 60.4 (CH_2CH_3), 27.0 (Me), 26.9 (Me), 14.3 (CH_2CH_3) ppm. HRMS: calcd. for $C_{20}H_{26}O_7$ $[M + H]^+$ 379.1751, found 379.1757; calcd. for $[M + Na]^+$ 401.1571, found 401.1577; calcd. for $[M + K]^+$ 417.1310, found 417.1319.

Data for **13**: R_f = 0.21 (EtOAc/petroleum ether, 1:3). m.p. 158–159 ºC. $[\alpha]_D^{20}$ = + 35 (c = 0.4 in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.30 (m, 5H, Ph), 6.06 (br. d, 1H, H-6), 5.83 (d, 1H, H-1, $J_{1,2}$ = 3.6 Hz), 4.87 (d, 1H, H-4, $J_{3,4}$ = 9.2 Hz), 4.84, 4.80 (dd, part A of ABX system, 1H, H-5'a, $J_{5'a,5'b}$ = 18.2, $J_{5'a,\ 6}$ = 1.6 Hz), 4.81, 4.78 (d, part A of AB system, 1H, H-a, OCH_2Ph, $J_{a,b}$ = 11.6 Hz), 4.72, 4.68 (d, part B of ABX system, 1H, H-5'b), 4.66 (t, 1H, H-2), 4.56, 4.53 (d, part B of AB system, 1H, H-b, OCH_2Ph), 3.65 (dd, 1H, H-3, $J_{2,3}$ = 4.1 Hz), 1.62 (s, 3H, Me), 1.39 (s, 3H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3 (C-7), 166.2 (C-5), 136.5 (Cq, Ph), 128.9, 128.7, 128.4 (*C*H, Ph), 116.1 (C-6), 113.8 (Cq, isopr.), 104.5 (C-1), 81.5 (C-3), 76.9 (C-2), 74.6 (C-4), 72.6 (OCH_2Ph), 70.9 (C-5'), 26.8 (Me), 26.5 (Me) ppm. HRMS: calcd. for $C_{18}H_{20}O_6$ $[M + H]^+$ 333.1333, found 333.1333.

Ethyl (5*Z*)-3-*O*-Allyl-5,6-dideoxy-5-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-D-*ribo*-5-enoheptofuranuronate (12) and 3-*O*-Allyl-5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*ribo*-5-enoheptofuranurono-7,5'-lactone (14): Wittig olefination of 3-*O*-allyl-1,2-

O-isopropylidene-α-D-*ribo*-hexofuranos-5-ulose (**8**, 0.163 g, 0.63 mmol) was completed within 2 h and gave **12** (0.023 g, 11%) as a colorless syrup and **14** (0.087g, 49%) as a white solid, after purification by CC (EtOAc/cyclohexane, 1:4). Data for **12**: R_f = 0.34 (EtOAc/ petroleum ether, 2:3). $[\alpha]_D^{20}$ = +3 (c = 0.3, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.10 (s, 1H, H-6), 5.92–5.81 (m, 1H, C*H* allylic), 5.80–5.74 (m, 2H, H-1, H-4), 5.30–5.17 (m, 2H, =CH_2 allylic), 4.64 (t, 1H, H-2, $J_{1,2} = J_{2,3}$ = 4.8 Hz), 4.35, 4.34, 4.31, 4.30 (dd, part A of ABX system, 1H, H-5'a, $J_{5'a,5'b}$ = 15.2, $J_{5'a,OH}$ = 3.8 Hz), 4.22–4.10 (m, 3H, H-5'b, CH_2CH$_3$, J = 7.1), 4.16, 4.14, 4.12, 4.11 (dd, part A of ABX system, 1H, H-a, OCH_2 allylic, $J_{a,b}$ = 13.4, $J_{a,H\text{-}all}$ = 6.1 Hz), 4.06, 4.04, 4.02, 4.01 (dd, part B of ABX system, 1H, H-b, OCH_2 allylic, $J_{b,H\text{-}all}$ = 5.6), 3.81 (dd, 1H, H-3, $J_{3,4}$ = 9.1 Hz), 3.36 (t, 1H, OH), 1.64 (s, 3H, Me), 1.37 (s, 3H, Me), 1,29 (t, 3H, CH$_2$CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9 (*C*O), 151.4 (C-5), 134.4 (*C*H allylic), 120.3 (C-6), 118.1 (=*C*H$_2$ allylic), 113.7 (Cq, isopr.), 104.1 (C-1), 81.4 (C-3), 77.9 (C-2), 75.2 (C-4), 71.8 (O*C*H$_2$ allylic), 63.1 (C-5'), 60.5 (*C*H$_2$CH$_3$), 27.0 (Me), 26.8 (Me), 14.3 (CH$_2$*C*H$_3$) ppm. HRMS: calcd. for $C_{16}H_{24}O_7$ [M + H]$^+$ 329.1595, found 329.1610; calcd. for [M + Na]$^+$ 351.1414, found 351.1403.

Data for **14**: R_f = 0.18 (EtOAc/petroleum ether, 1:3); mp: 64–66 ºC. $[\alpha]_D^{20}$ = +65 (c = 1.2, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.12 (br. s, 1H, H-6), 5.98–5.86 (m, 1H, C*H* allylic), 5.85 (d, 1H, H-1, $J_{1,2}$ = 3.5 Hz), 5.37–5.25 (m, 2H, =CH_2 allylic), 4.94, 4.89 (dd, part A of ABX system, 1H, H-5'a, $J_{5'a,5'b}$ = 18.2 Hz, $J_{5'a,6}$ = 1.8 Hz), 4.87–4.79 (m, 2H, H-4, H-5'b), 4.70 (t, 1H, H-2), 4.27, 4.26, 4.24, 4.22 (dd, part A of ABX system, 1H, H-a, OCH_2 allylic, $J_{a,b}$ = 12.4, $J_{a,H\text{-}all}$ = 5.6 Hz), 4.09, 4.07, 4.06, 4.04 (dd, part B of ABX system, 1H, H-b, OCH_2 allylic, $J_{b,H\text{-}all}$ = 6.3 Hz), 3.66 (dd, 1H, H-3, $J_{2,3}$ = 4.1, $J_{3,4}$ = 9.4 Hz), 1.61 (s, 3H, Me), 1.39 (s, 3H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.3 (C-7), 166.4 (C-5), 133.6 (*C*H allylic), 119.3 (=*C*H$_2$ allylic), 115.8 (C-6), 113.8 (Cq, isopr.), 104.5 (C-1), 82.0 (C-3), 77.0 (C-2), 74.5 (C-4), 71.9 (O*C*H$_2$ allylic), 71.0 (C-5'), 26.8 (Me), 26.5 (Me) ppm. HRMS: calcd. for $C_{14}H_{18}O_6$ [M + H]$^+$ 283.1176, found 283.1181.

General Procedure for the Synthesis of β-Hydroxy Lactones 15–16: To a mixture of previously activated granulated zinc 20 mesh (78 mg, 1.2 mmol) and hexofuranos-5-ulose (0.8 mmol) in anhydrous THF (0.6 mL) was added a solution of ethyl bromoacetate (0.13 mL, 1.1 mmol) in THF (0.7 mL) under argon. The mixture was

stirred at 50 ºC for 1 h 30 min. After cooling to room temp., a 10% HCl solution (8 mL, cooled at 0 ºC) was added. The mixture was extracted with CH_2Cl_2 (3×4 mL), the organic phase was neutralized with a diluted $NaHCO_3$ solution, washed with water and dried with anhydrous $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography (CC) on silica gel.

3-*O*-Benzyl-6-deoxy-5-*C*-hydroxymethyl-1,2-O-isopropylidene-α-L-*ido*-heptofuranurono-7,5'-lactone (15): 3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**5**, 0.25 g, 0. 8 mmol) gave **15** (0.041 g, 15%) as a colorless oil, after purification by CC (EtOAc/petroleum, 3:7). R_f = 0.44 (EtOAc/petroleum ether, 2:3). $[\alpha]_D^{20}$ = –51 (c = 0.9, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.31 (m, 5H, Ph), 6.01 (s, 1H, H-1, $J_{1,2}$ = 3.8 Hz), 4.76, 4.73 (d, part A of AB system, 1H, H-a, OCH_2Ph, $J_{a,b}$ = 11.7 Hz), 4.67 (d, 1H, H-2), 4.49, 4.46 (d, part B of AB system, 1H, H-b, OCH_2Ph), 4.42, 4.39 (d, part A of AB system, 1H, H-5'a, CH_2OCO, $J_{5'a,5'b}$ = 10.4 Hz), 4.25, 4.22 (d, part B of AB system, 1H, H-5'b, CH_2OCO), 4.21 (d, 1H, H-3), 4.14 (d, 1H, H-4, $J_{3,4}$ = 3.8 Hz), 2.68, 2.64 (d, part A of AB system, 1H, H-6a, $J_{6a,6b}$ = 17.5 Hz), 2.46, 2.42 (d, part B of AB system, 1H, H-6b), 1.49 (s, 3H, Me), 1.34 (s, 3H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8 (*C*O), 135.8 (Cq, Ph), 129.1, 128.9, 128.5 (*C*H, Ph), 112.2 (Cq, isopr.), 105.2 (C-1), 82.3 (C-3), 81.8 (C-2), 81.0 (C-4), 76.9 (C-5'), 76.6 (C-5), 72.2 (O*C*H$_2$Ph), 40.6 (C-6), 26.8 (Me), 26.2 (Me) ppm. HRMS: calcd. for $C_{18}H_{22}O_7$ $[M + H]^+$ 351.1438, found 351.1439.

3-*O*-Allyl-6-deoxy-5-*C*-hydroxymethyl-1,2-*O*-isopropylidene-α-L-*ido*-heptofuranurono-7,5'-lactone (16): 3-*O*-Allyl-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuranos-5-ulose (**6**, 0.22 g, 0. 86 mmol) gave **16** (0.048 g, 19%) as a colorless oil, after purification by CC (EtOAc/cyclohexane, 1:4). R_f = 0.22 (EtOAc/petroleum ether, 1:4). $[\alpha]_D^{20}$ = –21 (c = 1.1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00 (s, 1H, H-1, $J_{1,2}$ = 3.8 Hz), 5.94–5.82 (m, 1H, C*H* allylic), 5.38–5.28 (m, 2H, =CH_2 allylic), 4.60 (d, 1H, H-2), 4.48, 4.46 (d, part A of AB system, 1H, H-5'a, CH_2OCO, $J_{5'a,5'b}$ = 10.4 Hz), 4.32, 4.29 (d, part B of AB system, 1H, H-5'b, CH_2OCO), 4.26 (d, 1H, H-3, $J_{3,4}$ = 3.5 Hz), 4.24, 4.22, 4.21, 4.19 (dd, part A of ABX system, 1H, H-a, OCH_2 allylic, $J_{a,b}$ = 12.6, $J_{a,H\text{-}all}$ = 5.3 Hz), 4.11 (d, 1H, H-4), 4.03, 4.01, 4.00, 3.98 (dd, part B of ABX system, 1H, H-b, OCH_2 allylic, $J_{b,H\text{-}all}$ = 6.6 Hz), 2.85, 2.81 (d, part A of AB system, 1H,

H-6a, $J_{6a,6b}$ = 17.4 Hz), 2.61, 2.57 (d, part B of AB system, 1H, H-6b), 1.50 (s, 3H, Me), 1.34 (s, 3H, Me) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1 (*C*O), 132.7 (*C*H allylic), 119.8 (=*C*H_2 allylic), 112.3 (Cq, isopr.), 105.2 (C-1), 82.7 (C-4), 81.9 (C-2), 81.2 (C-3), 77.2 (C-5'), 76.8 (C-5), 71.2 (O*C*H_2 allylic), 40.8 (C-6), 26.9 (Me), 26.3 (Me) ppm. HRMS: calcd. for $C_{14}H_{20}O_7$ $[M + H]^+$ 301.1282, found 301.1287.

3-Deoxy-3-*C*-[(*E*)-(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-6-*O*-pivaloyl-α-D-*ribo*-hexofuranose (19) and 3-Deoxy-3-*C*-[(*E*)-(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-5,6-di-*O*-pivaloyl-α-D-*ribo*-hexofuranose (20): To a solution of 3-deoxy-3-*C*-[(*E*)-(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranose (**18b**, 66 mg, 0.23 mmol**)** in dry pyridine (1 mL) at 0 ºC was added a solution of pivaloyl chloride (0.25 mmol, 0.03 mL) in dry CH_2Cl_2 (0.4 mL), under N_2. The whole solution was kept whilst stirring at 0 ºC for 1 h. The solvent was then removed under vacuum. The residue was poured into water (10 mL) and extracted with CH_2Cl_2 (3 × 5 mL). Combined organic layers were washed with a sat. aq. $NaHCO_3$ solution, water and brine, and dried over $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by CC (EtOAc/petroleum ether, 1:4) to afford the mono-*O*-pivaloyl derivative **19** (69 mg, 81%) and the di-*O*-pivaloyl derivative **20** (6.5 mg, 7%) derivatives as colorless oils.

Data for **19**: R_f = 0.16 (EtOAc/petroleum ether, 1:4). $[\alpha]_D^{20}$ = +189 (c = 1.0, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.25 (t, 1H, H-3', $J_{2,3'} \sim J_{3',4} \sim$ 1.9 Hz), 5.91 (d, 1H, H-1, $J_{1,2}$ = 4.8 Hz), 5.66 (dt, 1H, H-4, $J_{2,4} \sim J_{3',4}$, $J_{4,5}$ = 5.9 Hz), 5.16 (dt, 1H, H-2), 4.27-4.16 (m, 3H, H-6a, C*H*$_2$CH$_3$, $J_{5,6a}$ = 3.6, $J_{6a,6b}$ = 11.7 Hz), 4.06 (dd, 1H, H-6b, $J_{5,6b}$ = 6.1 Hz), 3.89 (ddd, H-5), 1.43 (s, 3H, Me), 1.40 (s, 3H, Me), 1.31 (t, 3H, CH$_2$C*H*$_3$, J = 7.1 hz), 1.22 (br. s, 9H, Me, Piv) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.8 (*C*O, Piv), 166.6 (*C*O), 158.0 (C-3), 118.9 (C-3'), 113.9 (Cq, isopr.), 103.7 (C-1), 81.8 (C-2), 80.7 (C-4), 73.0 (C-5), 65.3 (C-6), 61.3 (*C*H$_2$CH$_3$), 39.0 (Cq, Piv), 28.0 (Me, isopr.), 27.9 (Me, isopr.), 27.3 (Me, Piv), 14.2 (CH$_2$*C*H$_3$) ppm. HRMS: calcd. for $C_{18}H_{28}O_8$ $[M + Na]^+$ 395.1677, found 395.1687.

Data for **20**: R_f = 0.61 (EtOAc/petroleum ether, 2:3). $[\alpha]_D^{20}$ = +18 (c = 0.3, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.19 (t, 1H, H-3', $J_{2,3'} \sim J_{3',4} \sim$ 1.9), 5.89 (d, 1H, H-1, $J_{1,2}$ = 4.7 Hz), 5.79 (dt, 1H, H-4, $J_{2,4} \sim J_{3',4}$, $J_{4,5}$ = 4.1 Hz), 5.25 (ddd, H-5), 5.12 (dt, 1H, H-2), 4.29-4.17 (m, 3H, H-6a, C*H*$_2$CH$_3$, $J_{5,6a}$ = 3.8, $J_{6a,6b}$ = 11.7 Hz), 4.10, 4.08,

4.07, 4.05 (dd, part B of ABX system, 1H, H-6b, $J_{5,6b}$ = 7.6 Hz), 1.42 (s, 3H, Me), 1.38 (s, 3H, Me), 1.29 (t, 3H, CH_2CH_3, J = 7.1 Hz), 1.24 (br. s, 9H, Me, Piv), 1.18 (br. s, 9H, Me, Piv) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.6 (*C*O, Piv), 165.0 (*C*O), 156.4 (C-3), 119.3 (C-3'), 113.8 (Cq, isopr.), 103.9 (C-1), 81.6 (C-2), 79.5 (C-4), 72.9 (C-5), 62.8 (C-6), 61.0 (CH_2CH_3), 38.9 (Cq, Piv), 38.6 (Cq, Piv), 28.0 (Me, isop), 27.9 (Me, isop), 27.3 (Me, Piv), 27.2 (Me, Piv), 14.2 (CH_2CH_3) ppm. HRMS: calcd. for $C_{23}H_{36}O_9$ $[M + H]^+$ 457.2432, found 457.2446; calcd. for $[M + Na]^+$ 479.2252, found 479.2267.

3-*C*-(Carboxymethylene)-3-deoxy-6-*O*-pivaloyl-α-D-*ribo*-hexopyranose-3',4-lactone (21): A solution of 3-deoxy-3-*C*-[(*E*)-(ethoxycarbonyl)methylene]-1,2-*O*-isopropylidene-6-*O*-pivaloyl-α-D-*ribo*-hexofuranose (**19**, 62 mg, 0.17 mmol) in aq. AcOH (70%, 1.46 mL) was stirred under reflux for 1 h 45 min. The solvent was coevaporated with toluene (3×) and the crude product was purified by CC (EtOAc/petroleum ether, 3:2) to afford **21** (28 mg, 58 %) as a colorless oil. R_f = 0.21 (EtOAc/petroleum ether, 4:1). $[\alpha]_D^{20}$ = –5 (c = 0.8, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, α anomer): δ = 6.15 (br. s, H-3'), 5.50 (d, H-1, $J_{1,2}$ = 3.8 Hz), 4.76 (d, H-4, $J_{4,5}$ = 9.2 Hz), 4.59 (br. d, H-2), 4.54, 4.53, 4.51, 4.50 (dd, part A of ABX system, H-6a, $J_{5,6a}$ = 2.5, $J_{6a,6b}$ = 12.2 Hz), 4.30, 4.29, 4.27, 4.26 (dd, part B of ABX system, H-6b, $J_{5,6b}$ = 4.6 Hz), 3.93 (ddd, H-5), 1.22 (s, Me, Piv.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, α anomer): δ = 178.7 (*C*O, Piv), 172.4 (*C*O, lact.), 168.8 (C-3), 114.8 (C-3'), 92.9 (C-1), 76.9 (C-4), 71.4 (C-5), 69.1 (C-2), (C-6), 39.2 (Cq, Piv), 27.3 (Me, Piv.) ppm. HRMS: calcd. for $C_{13}H_{18}O_7$ $[M + H]^+$ 287.1125, found 287.1134; calcd. for $[M + Na]^+$ 309.0945, found 309.0953.

3-*C*-(Carboxymethylene)-3-deoxy-D-*ribo*-hexopyranose-3',2-lactone (22):

Method A. To a solution of 3-deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose [18] (**17a**, 0.11 g, 0.33 mmol) in MeOH (1.8 mL) was added Amberlite IR-120 H^+ resin (35 mg). The mixture was moderately stirred under reflux overnight. After filtration of the resin and evaporation of the solvent, the crude product was purified by CC using AcOEt as eluent to afford **22** (60 mg, 90%) as a white solid.

Method B: Alternatively, an analogous procedure using Dowex-50W (H^+ form) resin led the reaction to completion within 2 h. After filtration of the resin and evaporation of

the solvent, compound **22** was crystallized from AcOEt (yield: 57%). R_f = 0.22 (EtOAc). m.p. 168–174 ºC. $[\alpha]_D^{20}$ = +192 (c 0.9, in MeOH). ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.56 (d, OH-1β, J = 5.6 Hz), 7.04 (d, OH-1α, J = 4.6 Hz), 6.00 (d, OH-4β, J = 5.8 Hz), 5.95–5.87 (m, H-3'α, H-3'β, OH-4α), 5.47 (t, H-1α), 4.96 (d, H-2α, $J_{1,2(\alpha)}$ = 4.1 Hz), 4.89 (t, OH-6β), 4.79 (t, OH-6α), 4.65 (d, H-2β, $J_{1,2(\beta)}$ = 7.1), 4.37–4.30 (m, H-1β, H-4α, H-4β), 3.79–3.52 (m, H-6aα, H-6aβ, H-6bα, H-6bβ, H-5α, $J_{5,6a\ (\beta)}$ = 5.3, $J_{6a,6b\ (\beta)}$ = 12.1, $J_{5,6a(\alpha)}$ = 5.3, $J_{6a,6b\ (\alpha)}$ = 11.6 Hz), 3.12 (ddd, H-5β) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO) δ = 172.9 (*C*O), 171.1 (C-3α), 111.7 (C-3'α, C-3'β), 98.7 (C-1β), 90.4 (C-1α), 82.0 (C-2β), 80.2 (C-5β), 78.6 (C-2α), 74.4 (C-5α), 66.1 (C-4β), 65.7 (C-4α), 60.1 (C-6α, C-6β) ppm. HRMS: calcd. for $C_8H_{10}O_6$ [M + H]$^+$ 203.0550, found 203.0550; calcd. for [M + Na]$^+$ 225.0370, found 225.0369; calcd. for [M + K]$^+$ 241.0109, found 241.0109. $C_8H_{10}O_6$ (202.16): C 47.53, H 4.99; found C 47.60, H, 4.90.

1,4,6-Tri-*O*-acetyl-3-*C*-(carboxymethylene)-3-deoxy-α,β-D-*ribo*-hexopyranose-3',2-lactone (23): To a solution of 3-*C*-(carboxymethylene)-3-deoxy-D-*ribo*-hexopyranose-3',2-lactone (68 mg, 0.34 mmol) in py (2 mL), was added Ac_2O (1 mL) and the mixture was stirred at room temp. for 5 min. After coevaporation with toluene (3×), the crude product was purified by CC on silica gel (EtOAc/petroleum ether, 1:1) to afford **23** (94 mg, 85%) as a colorless oil. R_f = 0.32 (EtOAc/petroleum ether, 1:1). $[\alpha]_D^{20}$ = +178 (c = 1.2, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.60 (d, H-1α, $J_{1,2}$ = 4.6 Hz), 6.02–5.96 (m, H-3'α, H-3'β), 5.71 (dd, H-4α, $J_{3',4(\alpha)}$ = 1.5, $J_{4,5(\alpha)}$ = 9.6 Hz), 5.66 (dd, H-4β, $J_{3',4(\beta)}$ = 1.5, $J_{4,5(\beta)}$ = 9.6 Hz), 5.40 (d, H-1β, $J_{1,2(\beta)}$ = 7.6 Hz), 5.10 (dd, H-2α, $J_{2,3'(\alpha)}$ = 1.5 Hz), 4.90 (dd, H-2β, $J_{2,3'(\beta)}$ = 1.5), 4.40–4.32 (m, H-6aα, H-6aβ) 4.24 (t, H-6bα, H-6bβ), 4.00 (ddd, H-5α), 3.77 (ddd, H-5β), 2.22 (s, Me, Ac, α, Me, Ac, β), 2.21 (s, Me, Ac, β), 2.11 (s, Me, Ac, α, Me, Ac, β), 2.09 (s, Me, Ac, α) ppm. ^{13}C NMR (100 MHz $CDCl_3$): δ = 171.0 (*C*O, Ac, α), 170.6 (*C*O, Ac, β, *C*O, lact., α, *C*O, lact., β), 169.1 (*C*O, Ac, β), 169.1 (*C*O, Ac, α), 168.7 (*C*O, Ac, β), 168.2 (*C*O, Ac, α), 163.2 (C-3β), 161.6 (C-3α), 115.3 (C-3'α) 114.7 (C-3'β), 95.4 (C-1β), 88.8 (C-1α), 78.9 (C-2β), 76.4 (C-2α), 76.2 (C-5β), 71.9 (C-5α), 66.4 (C-4β), 66.0 (C-4α), 61.4 (C-6α), 61.3 (C-6β), 20.8, 20.7, 20.7, 20.5 (Me, Ac) ppm. HRMS: calcd. for $C_{14}H_{16}O_9$ [M + H]$^+$ 329.0867, found 329.0864; calcd. for [M + Na]$^+$ 351.0687, found 351.0690; calcd. for [M + K]$^+$ 367.0426, found 367.0417.

Methyl 3-*C*-(carboxymethylene)-3-deoxy-α,β-D-*ribo*-hexopyranoside-3',2-lactone (24): To a solution of 3-deoxy-3-*C*-[(*Z*)-(ethoxycarbonyl)methylene]-1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranose [18] (0.14 g, 0.43 mmol) in MeOH (2 mL) was added Dowex-50W (H^+ form) resin (42 mg). The mixture was stirred under reflux overnight. After filtration of the resin and evaporation of the solvent, the crude product was purified by CC on silica-gel (EtOAc/petroleum ether, 7:3) to afford **24** (52 mg, 57%) as a colorless oil. R_f = 0.15 (EtOAc/petroleum ether, 7:3). $[\alpha]_D^{20}$ = +14 (c 0.5, in CH_2Cl_2). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 5.98 (t, H-3'β), 5.92 (t, H-3'α, J = 1.5 Hz), 5.24 (d, OH-4β, J = 6.3 Hz), 5.18–5.12 (m, H-1α, OH-4α), 4.97 (dd, 1H, H-2α, $J_{1,2(\alpha)}$ = 4.5 Hz), 4.66–4.57 (m, H-4α, H-4β, H-2β, $J_{1,2(\beta)}$ = 7.3 Hz), 4.24 (d, H-1β), 3.96-3.77 (m, H-6aα, H-6aβ, H-6bα,H-6bβ), 3.54–3.48 (m, Meβ, H-5α), 3.41 (s, Meα), 3.29 (ddd, H-5β) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 173.1 (*C*Oα), 172.6 (*C*Oβ), 171.9 (C-3β), 170.3 (C-3α), 113.3 (C-3'β), 112.8 (C-3'α), 106.3 (C-1β), 98.5 (C-1α), 81.5 (C-2β), 79.0 (C-2α), 75.8 (C-5α), 67.6 (C-4β), 67.0 (C-4α), 61.9 (C-6β), 61.8 (C-6α), 56.9 (Meβ), 55.3 (Meα) ppm. HRMS: calcd. for $C_9H_{12}O_6$ [M + H]$^+$ 217.0707, found 217.0700; calcd. for [M + Na]$^+$ 239.0526, found 239.0518.

1,4,6-Tri-*O*-acetyl-3-C-[(*R*)-(carboxy)hydroxymethyl]-α-D-glucopyranose-3',2-lactone (25a) and 1,4,6-Tri-*O*-acetyl-3-C-[(*R*)-(carboxy)hydroxymethyl]-β-D-glucopyranose-3',2-lactone (25b): To a solution of 1,4,6-tri-*O*-acetyl-3-*C*-(carboxymethylene)-3-deoxy-α,β-D-*ribo*-hexopyranose-3',2-lactone (94 mg, 0.29 mmol) in pyridine (2.3 mL), was added osmium tetroxide (97 mg, 0.38 mmol) and the mixture was stirred at room temp. for 15 min. Saturated $NaHSO_3$ solution (9 mL) and pyridine (3 mL) were added and the whole mixture was kept on stirring within 5 min to cleave the osmium complex. After extraction with $CHCl_3$ (3×15 mL), the combined organic layers were washed with water and dried with Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by CC (EtOAc/petroleum ether, 2:3) to afford the α-anomer **25a** (33 mg, 33%) and the β-anomer **25b** (23 mg, 23%) as white solids. Data for **25a**: R_f = 0.27 (EtOAc/petroleum ether, 2:3). m.p.: 181.1–183.2 °C. $[\alpha]_D^{20}$ = +87 (c 2.0, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.43 (d, 1H, H-1, $J_{1,2}$ = 5.3 Hz), 5.03 (d, 1H, H-4, $J_{4,5}$ = 10.4 Hz), 4.69 (s, 1H, OH), 4.67–4.63 (m, 2H, H-2, H-3'), 4.37, 4.36, 4.35, 4.33 (dd, part A of ABX system, 1H, H-6a, $J_{5,6a}$ = 4.1, $J_{6a,6b}$ = 12.5 Hz), 4.24, 4.24, 4.22, 4.21 (dd, part B of ABX system, 1H, H-6b, $J_{5,6b}$ = 2.3 Hz), 4.07

(ddd, 1H, H-5), 2.72-2.67 (m, 1H, OH), 2.17 (s, 3H, Ac), 2.14 (s, 3H, Ac), 2.11 (s, 3H, Ac) ppm.^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ = 87.5 (C-1), 77.7 (C-2), 72.6 (C-4), 69.6 (C-3'), 67.0 (C-5), 61.9 (C-6), 20.9, 20.8, 20.7 (3 × *C*H_3, Ac) ppm. HRMS: calcd. for $C_{14}H_{18}O_{11}$ [*M* + Na]$^+$ 385.0741, found 385.0753.

Data for **25b**: R_f = 0.33 (EtOAc/petroleum ether, 2:3). m.p.: 139.0–140.7 ºC. $[\alpha]_D^{20}$ = +35 (c 1.1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.54 (d, 1H, H-1, $J_{1,2}$ = 8.4 Hz), 5.00 (d, 1H, H-4, $J_{4,5}$ = 10.4 Hz), 4.63 (s, 1H, OH), 4.52 (d, 1H, H-3'), 4.46 (d, 1H, H-2), 4.36, 4.35, 4.34, 4.33 (dd, part A of ABX system, 1H, H-6a, $J_{5,6a}$ = 4.8, $J_{6a,6b}$ = 12.5 Hz), 4.27, 4.25 (dd, part B of ABX system, 1H, H-6b, $J_{5,6b}$ = 2.3 Hz), 3.90 (ddd, 1H, H-5), 2.81-2.76 (m, 1H, OH), 2.18 (s, 3H, Ac), 2.16 (s, 3H, Ac), 2.11 (s, 3H, Ac) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ = 92.6 (C-1), 81.0 (C-2), 73.1 (C-4), 72.7 (C-5), 69.4 (C-3'), 62.0 (C-6), 20.9, 20.8, 20.7 (3 × *C*H_3, Ac) ppm. HRMS: calcd. for $C_{14}H_{18}O_{11}$ [*M* + Na]$^+$ 385.0741, found 385.0740.

1,2-Di-*O*-acetyl-3-*C*-(carboxymethylene)-3-deoxy-α,β-D-*erythro*-pentopyranose-3',2-lactone (27): A solution of 5-*O*-TBDMS-3-deoxy-3-C-[(*E*)-(ethoxycarbonyl)-methylene]-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose [15] (**26b**, 51 mg, 0.14 mmol) in aq. AcOH (70%, 1.1 mL) was stirred under reflux for 1 h 30 min. The solvent was then removed under vacuum. Ac_2O (0.4 mL) and py (0.8 mL) were added to the residue and the mixture was stirred for 5 min. After coevaporation with toluene, the crude product was purified by CC on silica gel (EtOAc/petroleum ether, 1:3) to afford the title compound (26.3 mg, 74%) as a colorless oil. R_f = 0.23 (EtOAc/petroleum ether, 1:3). $[\alpha]_D^{20}$ = –12 (c 0.5, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.47 (d, H-1α, $J_{1,2(\alpha)}$ = 4.5 Hz), 6.05 (t, H-3'α, $J_{2,3'(\alpha)} \sim J_{3',4(\alpha)} \sim$ 2 Hz), 5.97 (t, H-3'β, $J_{2,3'(\beta)} \sim J_{3',4(\beta)} \sim$ 2.0 Hz), 5.78 (ddd, H-2α, $J_{2,3'(\alpha)}$ = 2.0, $J_{2,4\ (\alpha)}$ = 0.5 Hz), 5.69 (ddd, H-2β, $J_{1,2(\beta)}$ = 7.6, $J_{2,3'(\beta)}$ = 2.0, $J_{2,4(\beta)}$ = 0.5 Hz), 5.49 (d, H-1β, 5.02-4.96 (m, H-4α, H-4β), 4.57 (dd, H-5aβ, $J_{4,5a(\beta)}$ = 6.8, $J_{5a,5b(\beta)}$ = 10.8 Hz), 4.36 (dd, H-5aα, $J_{4,5a(\alpha)}$ = 6.8, $J_{5a,5b(\alpha)}$ = 10.8 Hz), 3.56 (t, H-5bα, $J_{4,5b(\alpha)} \sim J_{5a,5b(\alpha)}$ = 10.5 Hz), 3.28 (dd, H-5bβ, $J_{4,5b(\beta)}$ = 10.0 Hz) 2.20, 2.16, 2.16, 2.12 (4s, Me, Ac, α, β) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 114.9 (C-3'β) 114.8 (C-3'α), 94.7 (C-1β), 89.3 (C-1α), 76.0 (C-4β), 75.6 (C-4α), 69.7 (C-2β), 68.5 (C-5β), 68.3 (C-2α), 65.4 (C-5α), 20.9, 20.8, 20.6, 20.5 (Me, Ac) ppm. HRMS: calcd. for $C_{11}H_{12}O_7$ [*M* + Na]$^+$ 279.0475, found 279.0469.

4,6-Di-*O*-acetyl-2-bromo-2,3-dideoxy-D-erythro-hex-2-enono-1,5-lactone (29):

Method A: The protocol described in ref. [16] was used, except the number of equiv. of PCC, which was reduced to 2.5, and slight modifications concerning the work-up procedure. After total consumption of **28**, as indicated by TLC, the solvent was evaporated under reduced pressure. Ethyl ether was added to the residue, in order to precipitating the Cr^{III} species and the resulting mixture was filtered over a short Florisil pad. The filtrate was concentrated in vacuum and the crude was purified by CC on silica gel (EtOAc/petroleum ether, 3:7) to afford **29** in 43% yield (0.24 g, starting from 0.5 g of **28**) as a colorless oil. ^{1}H NMR spectroscopic data were in fully agreement with the reported data [16].

Method B. The oxidation step was carried out as follows. To the residue obtained from the first step in CH_2Cl_2 (6 mL), was added a mixture of PDC (1.38 g, 3.66 mmol) and Ac_2O (1.4 mL, 14.8 mmol) in CH_2Cl_2 (15 mL) at room temp. under argon. The whole mixture was stirred at room temp. for 30 h. After a similar work up than that described above and purification by CC, compound **29** was obtained in 31% yield (345 mg starting from 1 g of **28**).

2. Biological assays

The susceptibility of microorganisms to the unsaturated lactones **13**, **14**, **22**, **23**, **29**, **30** and **31** was evaluated by the disk diffusion method according to the standard procedure CLSI (Clinical Laboratory Standards Institute/National Committee for Clinical Laboratory Standards) [19, 20]. The microorganisms used in the tests belong to the American Type Culture Collection (ATCC) and Centraalbureau voor Schimmelcultures (CBS) collections, from United States and The Netherlands, respectively. Additional fungi kept in our lab were also used. The group of bacteria chosen for the study consisted of Gram-negative strains such as *Escherichia coli* (ATCC 8739) and *Pseudomonas aeruginosa* (ATCC 27853) and the following Gram-positive bacteria: *Bacillus cereus* (ATCC 11778), *Bacillus subtilis* (ATCC 6633), *Enterococcus faecalis* (ATCC 29212) and *Staphylococcus aureus* (ATCC 25923). For the antifungal bioassays, six fungi were tested: *Botrytis* spp., *Candida albicans* (ATCC 10231), *Colletotrichum coffeanum* (CBS 396.67), *Fusarium culmorum* (CBS 129.73), *Pyricularia oryzae* (CBS 433.70), and *Rhizopus* spp.. The culture medium and incubation temperature used for fungal growth was Potato Dextrose Agar and 25 ºC,

whereas for bacteria, Nutrient Agar incubated at 37ºC was used. Paper disks of 6.4 mm were placed on the agar and the solution of each substance (300 µg) in DMSO (15 µL) was applied on each disk. Chloramphenicol was used as control for all bacteria tested and *C. albicans*, whereas actidione was used for the filamentous fungi. After incubation, the nearest diameter of the inhibition zone was measured. Zones less than 15 mm in diameter and uniform growth in the disk were considered indicative of weak antimicrobial activity; 15-20, moderate activity. Each sample was tested in three equivalent experiments.

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2.2. Thiopyranose Derivatives Containing an α,β-Unsaturated Carbonyl Functionality

This subchapter includes the paper:

"Synthetic Approaches to Novel Thiosugar Scaffolds Containing α,β-Unsaturated Carbonyl Groups", Xavier, N. M.; Madeira, P. J. A.; Florêncio, M. H., Rauter, A. P. *Eur. J. Org. Chem.* **2009**, *2009*, 4983−4991.

and shows the synthesis of new classes of thiosugar derivatives containing a conjugated carbonyl function. The methodology previously developed for pyranose-fused butenolides was employed to attain thiopyranose-based bicyclic analogues. Moreover, the synthesis of an α,β-unsaturated 5-thiopyranulose was achieved using a masked 3-ulose derived from 1,2:5,6-di-*O*-isopropylidene-α-D-ribo-hexofuranos-3-ulose as precursor.

The co-autors Madeira, P. J. A. and Florêncio, M. H. were responsible for the HRMS analysis.

Eur. J. Org. Chem. **2009**, *2009*, 4983−4991

Synthetic Approaches to Novel Thiosugar Scaffolds Containing α,β-Unsaturated Carbonyl Groups

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Keywords: Carbohydrates / Sulfur heterocycles / Lactones / Enones / Ring expansion / Thiosugars

Abstract

The synthesis of new classes of highly functionalized thiosugar derivatives containing α,β-unsaturated carbonyl functions has been accomplished through simple and efficient strategies. 5-Thiosugar-fused butenolides and a 5-thiohex-1-enopyranos-3-ulose were constructed from easily available starting 3-uloses by practical and reliable approaches. The reaction sequence used for the bicyclic fused derivatives involved Wittig olefination of protected pento- or hexofuranos-3-uloses, introduction of a sulfhydryl group at C-5 of the intermediate unsaturated ester and acid-promoted deprotection, which allowed intramolecular lactonization and conversion into the 5-thiopyranose form. For the synthesis of a 5-thio-hex-1-enopyranos-3-ulose, a sulfhydryl functionality was introduced at C-5 on a masked 3-ulose derived from 1,2:5,6-di-*O*-isopropylidene-α-D-ribo-hexofuranos-3-ulose. Acid hydrolysis displaced the equilibrium towards the 5-thiopentopyranos-3-ulose, which on pyridine-mediated acetylation underwent 1,2–elimination of acetic acid to give the desired α,β-unsaturated 5-thiopyranulose. This straightforward pathway provided the target compound in 37% overall yield.

Introduction

Thiosugars containing sulfur as a heteroatom in the ring possess interesting chemical and biological properties and have attained considerable importance in glycobiology and in drug design as glycosidase inhibitors or as potential anticancer and anti-HIV agents [1, 2]. The different electronic properties of the sulfur and oxygen atoms (i.e., electronegativity and polarizability), and the changes in flexibility and conformation of the ring when an oxygen atom is replaced by sulfur, together with the distinct chemical reactivity of the sulfide function relative to the corresponding ether moiety, are assumed to contribute to the differences in the biological properties between thiosugars and their carbohydrate analogues [3, 4].

A few examples of naturally occurring thiosugars have appeared in the literature [2]; the first isolated compound was 5-thio-D-mannose, from the marine sponge *Clathria pyramida*, in 1987 [5]. Since the first synthesis of 5-thio-α-D-xylopyranose in 1961 [6], a variety of approaches for the preparation of thiosugars by transformation of carbohydrate or non-carbohydrate precursors have been developed, and some reviews covering the methodologies have been published [3, 7].

Owing to their potential value as bioactive compounds, the search for new classes of thiosugars remains highly relevant. In this context we turned our attention to the synthesis of thiosugar derivatives comprising α,β-unsaturated carbonyl functions, such as ketones and lactones. This functionality possesses inherent bioactivity due to its ability to undergo Michael addition of enzymes' nucleophilic components, specially cysteine sulfhydryl groups [8, 9]. Moreover, sugars containing such systems are building blocks of high synthetic versatility and have been used as intermediates for a variety of important sugar derivatives, including disaccharides, branched-chain sugars, and bioactive natural products [10]. In particular, previous contributions in this field from our research group have shown the efficacy of furanose C-C-linked α,β-unsaturated γ-lactones as antifungal [11] and insecticidal agents [12]. In addition, we were also able to use sugar-fused unsaturated lactones as starting materials for the synthesis of the sugar moiety, and its epimer, contained in miharamycins [13],

antibiotics known as potent inhibitors of *Pyricularia oryzae*, which produces the rice blast disease and is considered a bioterrorism agent.

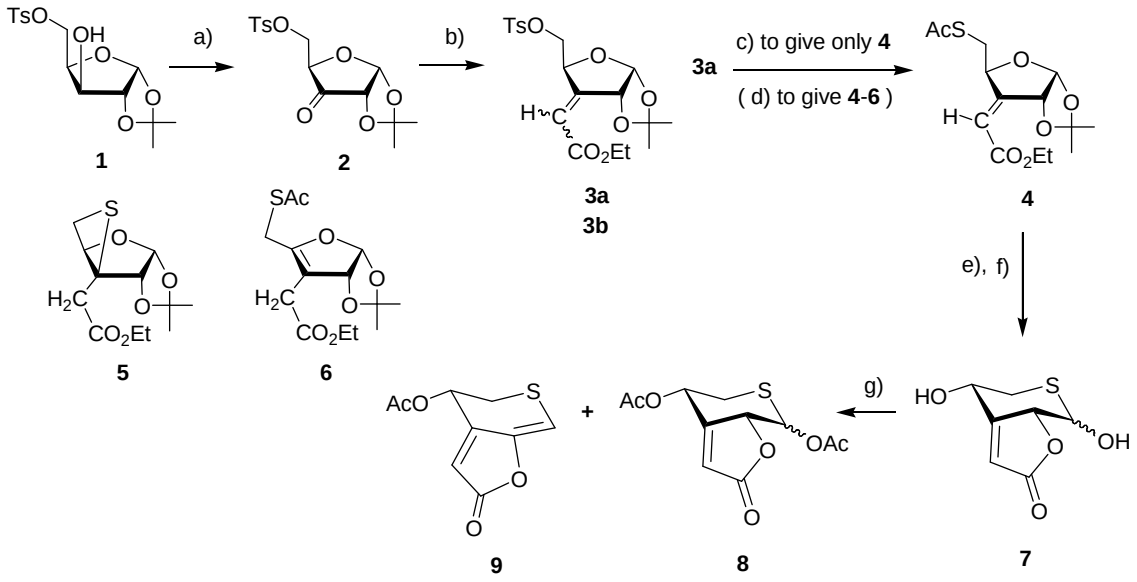
Combining thiosugar units to α,β-unsaturated carbonyl systems may therefore be a valuable tool for the design of new potentially biologically active substances, also providing highly functionalized templates for the synthesis of new thiosugar derivatives. The key structural feature of thiolactomycin and its analogues, based on an unsaturated thiolactone moiety, and their pharmacological properties, namely activity against bacteria (e.g., *Mycobacterium tuberculosis*) [14] and parasitic organisms (e.g., *Trypanosoma sp.* and *Plasmodium falciparum*) [15], additionally support these considerations.

With these motivations in mind we envisioned the synthesis of new thiosugar scaffolds containing such unsaturated system, namely, 5-thiopyranose-fused butenolides and a 1-eno-5-thiopentopyranos-3-ulose. For this purpose, easily available furanos-3-uloses were used as starting materials and the methodologies used were based on intramolecular cyclization approaches, taking advantage of the ability of the free sugars to undergo furanose-pyranose isomerization. For the synthesis of thiosugar-fused butenolides we explored our recently reported Wittig olefination/intramolecular lactonization method [16], with the introduction of additional sulfhydryl functionality at C-5 of the intermediate α,β-unsaturated ester. The strategy for the preparation of a 5-thiohex-1-enopyranos-3-ulose was based on the conversion of a hemiacetal, derived from 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose by partial hydrolysis and intramolecular cyclization of the resulting primary alcohol with the carbonyl group, into the corresponding 5-SH analogue, followed by acid removal of 1,2-*O*-isopropylidene group. Under these reaction conditions, the equilibrium between the hemiacetal and its ulose isomer and the furanose–pyranose equilibrium favoured the formation of the 5-thiopyranos-3-ulose, which by acetylation/1,2-elimination, gave the target α,β-unsaturated 5-thiopyranulose.

Results and Discussion

1. Thiopyranose-fused butenolides

The synthesis of a butenolide 2,3-fused to a 5-thio pentopyranose unit started with the commercially available 1,2-*O*-isopropylidene-α-D-xylofuranose, which was converted into the 5-*O*-tosyl derivative **1** [17] (Scheme 1) as a key intermediate for the introduction of a 5-thio group. Oxidation of **1** with PDC/Ac_2O afforded the 3-ulose **2** along with its hydrate in 77% yield [18]. Wittig-type reaction of **2** with the stabilized ylide [(ethoxycarbonyl)methylene]triphenylphosphorane gave the (*Z*)-α,β-unsaturated ester **3a** as the main product (77%) together with the *E*-adduct **3b** (17%). Substitution of the tosylate of **3a** by treatment with potassium thioacetate was efficiently achieved in DMF at 40 ºC, giving the desired product **4** in 84% yield. Use of a higher reaction temperature (90 ºC) also led to the formation of the thietane derivative **5**, resulting from Michael addition, and of the allylic rearrangement product **6**, both of which were inseparable from **4** by chromatography and were identified by NMR analysis of the mixture. Deacetylation and ester hydrolysis of **4** with sodium hydroxide in aq. methanol was followed by treatment with aq. acetic acid (70%) under reflux to cleave the 1,2-*O*-isopropylidene group. Concomitant isomerization and intramolecular lactonization furnished the target 5-thiosugar-fused butenolide **7** in 35% overall yield. In the ^{13}C NMR spectrum of **7**, the signal at δ = 174.8 ppm for the carbonyl group is consistent with an α,β-unsaturated lactone skeleton. Subsequent acetylation of **7** with Ac_2O in pyridine, provided the corresponding diacetate derivative **8** as a mixture of both anomers (α/β ratio 1:0.3) in 80% yield, together with traces of the 5-thioglycal-fused butenolide **9**. The structure of the elimination product **9** was supported by ^1H NMR and HRMS data. A long-range coupling between H-1 and H-3' with a constant of 1.5 Hz and the high chemical shift of H-1 (δ = 6.47 ppm) is indicative of the conjugated system of **9**.



Scheme 1. Reactions and conditions: a) PDC/Ac_2O, CH_2Cl_2, reflux, 2 h 30 min, 77%; b) $Ph_3P{=}CHCO_2Et$, $CHCl_3$, reflux, 1h, 77% (**3a**) and 17% (**3b**); c) KSAc, DMF, 40 ºC, 1 h 45 min, 84%; d) KSAc, DMF, 90 ºC, 2 h; e) NaOH, MeOH/H_2O, room temp., 15 min; f) AcOH 70% aq., reflux, 2 h, 35%, 2 steps; g) Ac_2O, py, room temp., 5 min, 80% (**8**) and traces of **9**.

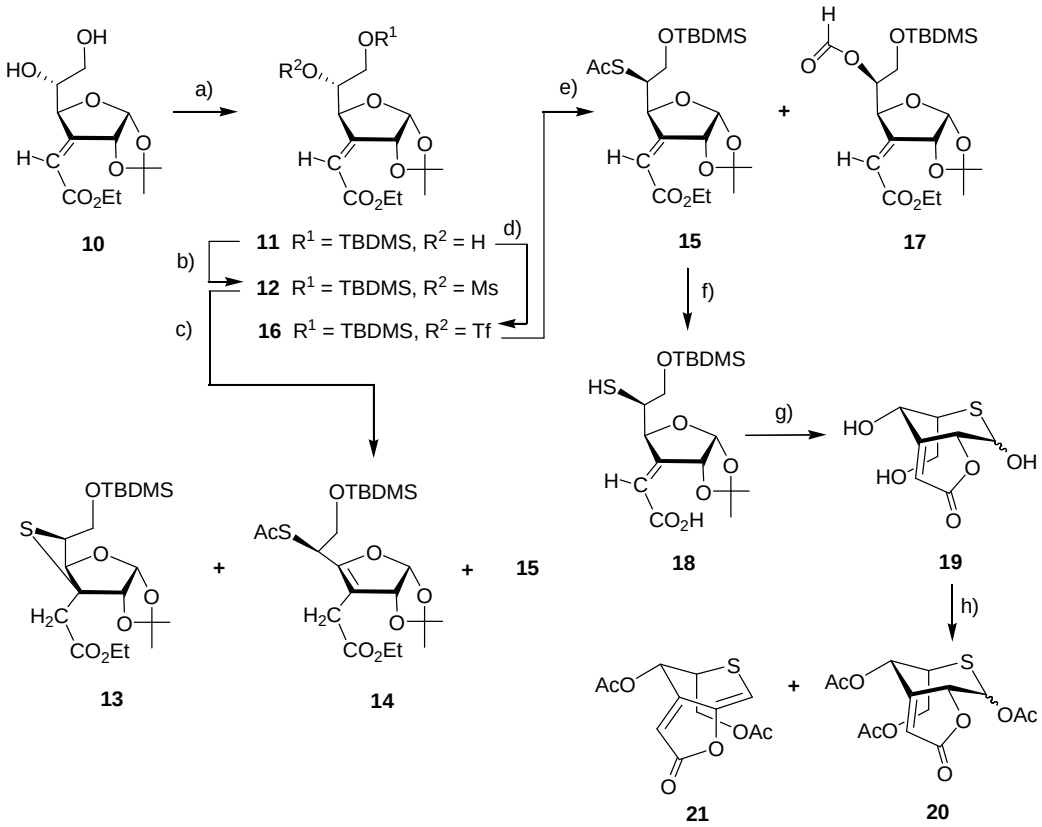
The feasibility and scope of this approach were then studied for the preparation of 5-thiohexopyranose-fused butenolides. The 5,6-diol **10** was prepared by Wittig olefination of 1,2;5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose, followed by selective hydrolysis of the primary acetonide as described previously [16a]. Silylation of the primary hydroxyl group (Scheme 2) was carried out with *tert*-butyldimethylsilyl chloride (TBDMSCl) and a catalytic amount of 4-dimethylaminopyridine (DMAP) in py (15 h) providing compound **11** (87%). Other standard methods such as imidazole in DMF (16%) and Et_3N/cat. DMAP in CH_2Cl_2 (42%) were less efficient. Mesylation, chosen to avoid possible steric hindrance caused by the *O*-TBDMS group, was achieved by treatment of **11** with methanesulfonyl chloride in pyridine, giving **12** in 95% yield. A high temperature (90 ºC) was required to substitute the mesylate by a thioacetate in DMF. The desired compound **15** was obtained in 24% yield together with the furanose-fused thietane **13** (15%) and **14** (19%) formed by migration of the exocyclic double bond.

Separation of **14** from **15** could not be achieved by column chromatography. To overcome this drawback, a one-pot, two-step procedure consisting on triflation/nucleophilic substitution was employed. Treatment of **11** with trifluoromethanesulfonic anhydride (Tf_2O)/py and then of the crude triflate **16** with potassium thioacetate in DMF gave **15** in modest yield (25%), together with a small amount of the 5-*O*-formyl derivative **17** (6%). The structure of **17** was established by NMR spectroscopy and HRMS. In the ^{1}H NMR spectrum a broad triplet for H-5 appeared at rather low field (δ = 5.21 ppm) and COSY experiments showed a weak coupling with the formyl proton (δ = 8.04 ppm). The ^{13}C NMR spectrum showed a quaternary carbon atom at δ = 164.8 ppm, corresponding to the *O*-formyl carbonyl group. The unexpected formation of **17** can be explained by a reaction of the triflate **16** and the solvent DMF. The formed iminium intermediate is readily converted into the formate **17** by hydrolysis during the workup (Scheme 3). A formylation method under similar conditions has been described previously [19].

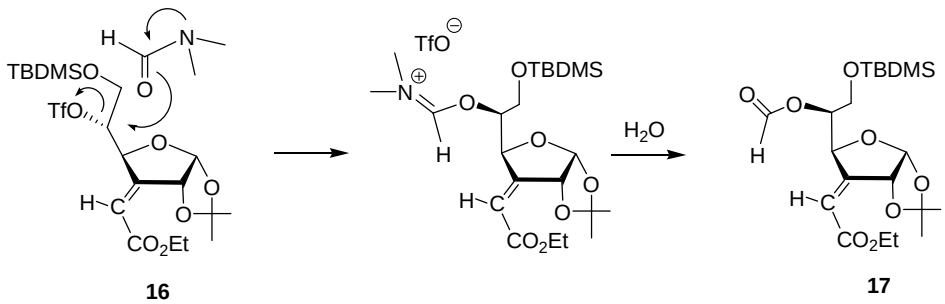
Although the yield of **15** was not improved by the second approach, separation was easily achieved by column chromatography. Compound **15** was treated with NaOH in aq. methanol to provide the corresponding α,β-unsaturated acid derivative **18**, containing a free sulfhydryl group at C-5, in 66% yield. Further hydrolysis of **18** with aq. TFA (60%) at 40 ºC afforded the desired 5-thiosugar-fused butenolide **19** (quantitative). The ^{13}C NMR spectrum showed the resonance of the carbonyl carbon of the lactone moiety at δ = 172.3 ppm.

In contrast with the reaction described above, acetylation of **19** under conditions similar to those used for the analogous compound **7** (Scheme 1) proceeded with elimination to give the thioglycal-fused butenolide **21**, isolated in 82% yield. The triacetate derivative **20** was obtained only in trace amounts and was inseparably contaminated with compound **21,** as determined by mass spectrometry. The difference in the reaction modes found for compounds **7** and **19** may be explained either by electronic or conformational factors. In both bicyclic compounds **8** and **20**, elimination at C1-C2, results in a highly stable α,β,γ,δ-unsaturated carbonyl system. The main driving force for the conversion of **20** into **21**, however, is the presence of a pseudoaxial acetyloxymethyl group at C-5 in **20**, which further destabilizes the distorted chair conformation of the thiopyranose ring. Elimination from **20** to give the corresponding

thioglycal **21**, which may adopt a *sofa* conformation, therefore occurs to overcome the steric destabilizing effect of the C-5 substituent.



Scheme 2. Reactions and conditions: a) TBDMSCl, py, catalytic DMAP, room temp., 15h, 87%; b) MsCl, py, 0 ºC to room temp., 40 min, 95%; c) KSAc, DMF, 90 ºC, 24 h, 15% (**13**), 19% (**14**) and 24% (**15**); d) Tf_2O, py, CH_2Cl_2, –5 ºC, 15 min; e) KSAc, DMF, room temp., 1 h, 25% (**15**) and 6% (**17**), two steps; f) NaOH, MeOH/H_2O, room temp., 1 h, 66%; g) TFA 60% aq., 40 ºC, 20 min, quantitative; h) Ac_2O, py, room temp., 5 min, 82% (**21**) and traces of **20**.

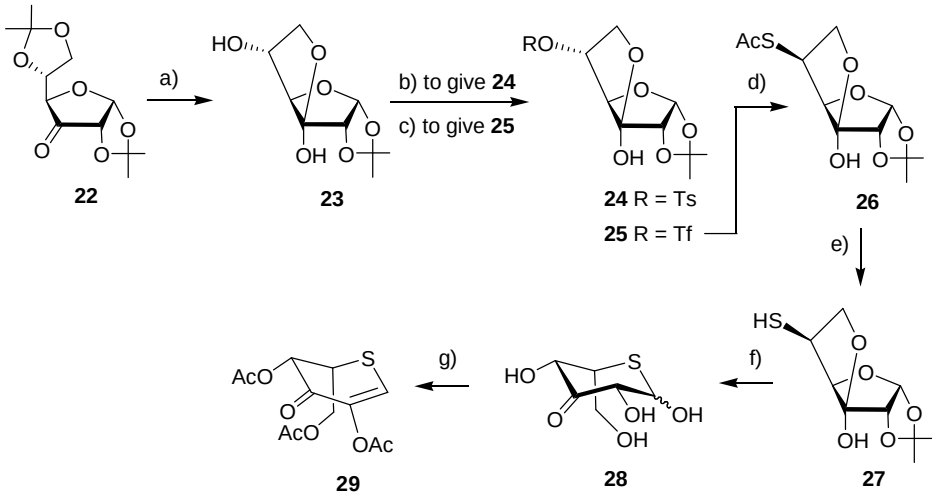


Scheme 3. Possible mechanism for the formation of the by-product **17**.

2. Synthesis of a Pyranoid Thiosugar Containing an α,β-Unsaturated Ketone Functionality

Synthesis of a 5-thio-hex-1-enopyranos-3-ulose was accomplished by starting from the key intermediate hemiacetal **23** [20], obtained by selective hydrolysis of 1,2;5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose **22** and subsequent cyclization of the 5,6-diol formed (Scheme 4). In order to introduce a sulfur functionality at C-5, the synthesis of the tosylated derivative **24** was attempted. However, the conversion was slow and compound **24** was obtained only in 34% yield after 40 h. Moreover, substitution of **24** with KSAc failed and no conversion was observed by TLC after 48 h at 40 ºC. Increasing the temperature to 70 ºC did not significantly improve the conversion and at 90 ºC, decomposition was observed by TLC.

Instead, **23** was triflated and the crude triflate **25** was directly treated with KSAc to give the desired 5-*S*-acetyl derivative **26** in 47% yield. Deacetylation with NaOH in aq. methanol afforded **27** in 90% yield. Treatment of this with aq. TFA (60%) produced the thiohexopyran-3-ulose **28** in quantitative yield as an α/β anomeric mixture. Subsequent acetylation and in situ β-elimination with Ac_2O in pyridine gave the target thio sugar-derived enone **29** in a nearly quantitative yield. This is consistent with the observation reported by Lichtenthaler and co-workers that β-acylated hexopyranuloses are prone to undergo β-elimination [21]. In accordance with the NMR spectroscopic data reported for sugar enones, the resonance of the C-3 carbonyl C-atom in the ^{13}C NMR spectrum of **29** appeared at δ = 182.5 ppm, whereas in the ^{1}H NMR spectrum a long-range coupling between H-1 and H-5 (J = 1.5 Hz) was observed [21b].



Scheme 4. Reactions and conditions: a) AcOH, 60% aq., room temp., 15 h, 92%; b) TsCl, py, room temp., 40 h, 34%; c) Tf_2O, py, CH_2Cl_2, –5 ºC, 10 min; d) KSAc, DMF, room temp., 1 h 15 min, 47%, two steps; e) NaOH, MeOH/H_2O, room temp., 5 min, 90%; f) TFA 60% aq., 40 ºC, 15 min, quantitative; g) Ac_2O, py, room temp., 5 min, 94%.

Conclusions

This contribution has demonstrated synthetic approaches for new classes of highly functionalized thiosugar derivatives containing α,β-unsaturated carbonyl moieties, such as lactones and ketones, through the use of easily available furanos-3-uloses as starting materials. The methodologies include the introduction of a sulfhydryl group at C-5 on appropriate furanose intermediates, such as an unsaturated ester and a hemiacetal sugar, and take advantage of the furanose-pyranose equilibrium. The synthesised molecules are valuable intermediates for further chemical transformations, in particular for syntheses of miharamycins analogues. In addition these compounds are potential bioactive candidates, in view of the biological profiles of the structural units involved.

Experimental Section

General Methods: Melting points were determined with a Stuart Scientific SMP 3 apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 343 polarimeter at 20 ºC. ^{1}H and ^{13}C NMR spectra were recorded with a BRUKER Avance

400 spectrometer operating at 400.13 MHz for ^{1}H or 100.62 MHz for ^{13}C. Chemical shifts are expressed in parts per million and are reported relative to internal TMS, in the case of $CDCl_3$, or relative to the respective solvent peak as reference. HRMS spectra were acquired with an Apex Ultra FTICR Mass Spectrometer fitted with an Apollo II Dual ESI/MALDI ion source, from Bruker Daltonics, and a 7T actively shielded magnet from Magnex Scientific.

All reactions were monitored by TLC on Merck 60 F_{254} silica gel aluminium plates with detection under UV light (254 nm) and/or by spraying with a solution of 10% H_2SO_4 in EtOH or with a solution of 0.2% (w/v) cerium(IV) sulphate/5% ammonium molybdate in aq. H_2SO_4 (6%). Column chromatography (CC) was carried out on silica gel 60 G (0.040–0.063 mm, E. Merck).

1,2-*O*-Isopropylidene-5-*O*-tosyl-α-D-*erythro*-pentofuranos-3-ulose (2): Ac_2O (1.4 mL) and PDC (1.44 g, 3.83 mmol) were added under argon to a solution of 1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose (**1**, 1.68 g, 4.88 mmol) [17] in dry CH_2Cl_2 (24 mL). The resulting mixture was stirred under reflux for 2 h 30 min and was then allowed to cool to room temp. The solvent was removed in vacuum. EtOAc (15 mL) was added to the residue and the mixture was filtered through a short pad of Florisil. After evaporation of the solvent, the crude product was purified by CC (EtOAc/petroleum ether, 1:1) to afford **2** as colorless oil, along with its hydrate in a 1:0.3 ratio (1.29 g, 77%). R_f = 0.25 (EtOAc/petroleum ether, 1:1).^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, 2H, H-a, Ts, J = 8.1 Hz), 7.37 (d, 2H, H-b, Ts), 6.04 (d, 1H, H-1, $J_{1,2}$ = 4.3 Hz), 4.51 (t, 1H, H-4), 4.35 (d, 1H, H-2), 4.31 (dd, part A of aBX system, 1H, H-5a, $J_{4,5a}$ = 2.5, $J_{5a,5b}$ = 11.1 Hz), 4.19 (dd, part B of ABX system, 1H, H-5b, $J_{4,5b}$ = 3.0 Hz), 2.46 (s, 3H, Me, Ts), 1.44 (s, 3H, Me, isopr.), 1.40 (s, 3H, Me, isopr.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.7 (*C*O), 145.4 (Cq-a, Ts), 132.4 (Cq-b), 130.1 (CH-b, Ts), 127.9 (CH-a, Ts), 114.5 (Cq, isopr.*)* 103.2 (C-1), 76.8 (C-4), 76.0 (C-2), 68.1 (C-5), 27.4 (Me, isopr.), 27.0 (Me, isopr.), 21.6 (Me, Ts) ppm. HRMS: calcd. for $C_{15}H_{18}O_7S$ $[M + Na]^+$ 365.0665, found 365.0673. Hydrate, HRMS: calcd. for $C_{15}H_{20}O_8S$ $[M + Na]^+$ 383.0771, found 383.0779.

Ethyl (3*Z*)-(3-Deoxy-1,2-*O*-isopropylidene-6-*O*-tosyl-α-D-*erythro*-pentofuranos-3-ylidene)acetate (3a) and Ethyl (3*E*)-(3-Deoxy-1,2-*O*-isopropylidene-6-*O*-tosyl-α-D-*erythro*-pentofuranos-3-ylidene)acetate (3b): [(Ethoxycarbonyl)methylene]-triphenylphosphorane (0.47 g, 1.35 mmol) was added to a solution of the 3-ulose **2** (0.35 g, 1.03 mmol) in dry $CHCl_3$ (8.3 mL). The mixture was stirred under reflux for 1 h. After evaporation of the solvent, the residue was purified by column chromatography (EtOAc/petroleum ether, 1:8 then 1:6) to afford the (*Z*)-adduct **3a** (0.329 g, 77%) and its (*E*)-isomer **3b** (0.074 g, 17%) as colorless oils.

Data for **3a**: R_f = 0.21 (EtOAc/petroleum ether, 1:8). $[\alpha]_D^{20}$ = +147 (c = 1.4, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.78 (d, 2H, H-a, Ts, J = 8.1 Hz), 7.36 (d, 2H, H-b, Ts), 5.83 (t, 1H, H-3', $J_{2,3'} = J_{3'4}$ = 1.8 Hz), 5.79 (d, 1H, H-1, $J_{1,2}$ = 4.0 Hz), 5.67 (dt, 1H, H-2, $J_{2,3'} = J_{2,4}$), 4.98–4.93 (m, 1H, H-4), 4.28–4.21 (m, 3H, CH_2CH$_3$, H-5a, J = 7.1 Hz), 4.12 (dd, 1H, H-5b, $J_{4,5b}$ = 3.5, $J_{5a,5b}$ = 11.1 Hz), 2.46 (s, 3H, Me, Ts), 1.45 (s, 3H, Me, isopr.), 1.40 (s, 3H, Me, isopr.), 1.32 (t, 3H, CH$_2$CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.5 (*C*O), 153.4 (C-3), 145.4 (Cq-a, Ts), 132.4 (Cq-b), 130.1 (CH-b, Ts), 128.1 (CH-a, Ts), 117.8 (C-3'), 113.3 (Cq, isopr.), 105.2 (C-1), 78.2 (C-2, C-4), 69.4 (C-5), 61.1 (*C*H$_2$CH$_3$), 27.5 (Me, isopr.), 27.2 (Me, isopr.), 21.8 (Me, Ts), 14.3 (CH$_2$*C*H$_3$) ppm. HRMS: calcd. for $C_{19}H_{24}O_8S$ [M + Na]$^+$ 435.1084, found 435.1082.

Data for **3b**: R_f = 0.16 (EtOAc/petroleum ether, 1:6). $[\alpha]_D^{20}$ = +153 (c = 1.0, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, 2H, H-a, Ts, J = 8.1 Hz), 7.34 (d, 2H, H-b, Ts), 6.09 (t, 1H, H-3', $J_{2,3'} = J_{3'4}$ = 1.8 Hz), 5.85 (d, 1H, H-1, $J_{1,2}$ = 4.6 Hz), 5.63–5.60 (m, 1H, H-4), 5.06 (dt, 1H, H-2, $J_{2,3'} = J_{2,4}$), 4.46 (dd, 1H, H-5a, $J_{4,5a}$ = 1.8, $J_{5a,5b}$ = 10.4 Hz), 4.20–4.09 (m, 3H, CH_2CH$_3$, H-5b, J = 7.1, $J_{4,5b}$ = 2.0 Hz) 2.45 (s, 3H, Me, Ts), 1.41 (s, 3H, Me, isopr.), 1.36 (s, 3H, Me, isopr.), 1.28 (t, 3H, CH$_2$CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3 (*C*O), 157.4 (C-3), 145.2 (Cq-a, Ts), 132.6 (Cq-b), 130.0 (CH-b, Ts), 128.0 (CH-a, Ts), 118.5 (C-3'), 113.6 (Cq, isopr.), 104.5 (C-1), 81.7 (C-2), 79.3 (C-4), 71.8 (C-5), 60.9 (*C*H$_2$CH$_3$), 27.9 (Me, isopr.), 27.8 (Me, isopr.), 21.8 (Me, Ts), 14.2 (CH$_2$*C*H$_3$) ppm. HRMS: calcd. for $C_{19}H_{24}O_8S$ [M + Na]$^+$ 435.1084, found 435.1094.

Ethyl (3*Z*)-(5-*S*-Acetyl-3-deoxy-1,2-*O*-isopropylidene-5-thio-α-D-*erythro*-pentofuranos-3-ylidene)acetate (4): Potassium thioacetate (34 mg, 0.30 mmol) was added under argon to a solution of ethyl (3*Z*)-(3-deoxy-1,2-*O*-isopropylidene-6-*O*-tosyl-

α-D-*erythro*-pentofuranos-3-ylidene)acetate (**3a**, 0.10 g, 0.25 mmol**)** in anhydrous DMF (2.5 mL). The whole solution was stirred at 40 ºC for 1 h 45 min. Water was added (12 mL) and the organic phase was extracted with EtOAc (3×3 mL). The combined organic layers were washed with water and dried with $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by CC (EtOAc/ petroleum ether, 1:11) to afford **4** (66 mg, 84%) as a colorless oil. R_f = 0.35 (EtOAc/petroleum ether, 1:4). $[\alpha]_D^{20}$ = +105 (c = 1.1, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.94 (t, 1H, H-3', $J_{2,3'} = J_{3',4}$ = 1.5 Hz), 5.88 (d, 1H, H-1, $J_{1,2}$ = 4.0 Hz), 5.72 (dt, 1H, H-2, $J_{2,3'} = J_{2,4}$), 5.01–4.96 (m, 1H, H-4), 4.28–4.21 (m, 2H, CH_2CH$_3$, J = 7.1 Hz), 3.41 (dd, part A of ABX system, 1H, H-5a, $J_{4,5a}$ = 3.8, $J_{5a,5b}$ = 14.1 Hz), 3.09 (dd, part B of ABX system, 1H, H-5b, $J_{4,5b}$ = 6.3 Hz), 2.36 (s, 3H, Me, SAc), 1.48 (s, 3H, Me, isopr.), 1.41 (s, 3H, Me, isopr.), 1.31 (t, 3H, CH$_2$CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.9 (*C*O, SAc), 164.9 (*C*O), 156.0 (C-3), 117.1 (C-3'), 112.9 (Cq, isopr.), 104.8 (C-1), 78.6 (C-4), 78.2 (C-2), 61.0 (*C*H$_2$CH$_3$), 32.1 (C-5), 30.6 (Me, SAc), 27.4 (Me, isopr.), 27.2 (Me, isopr.), 14.3 (CH$_2$*C*H$_3$) ppm. HRMS: calcd. for $C_{14}H_{20}O_6S$ [M + Na]$^+$ 339.0872, found 339.0867.

Ethyl (3,5-Anhydro-1,2-*O*-isopropylidene-5-thio-α-D-*erythro*-pentofuranos-3-*C*-yl) acetate (5) and Ethyl (5-*S*-Acetyl-3-deoxy-1,2-O-isopropylidene-5-thio-α-D-*glycero*-pent-3-enofuranos-3-*C*-yl)acetate (6): These compounds were obtained in an inseparable mixture also containing **4** (ratio 1:2:0.8, **4**/**5**/**6**, 38 mg starting from 49 mg of **3a**) after a similar procedure to that described previously for compound **4**, but with reaction being carried out at 90 ºC.

Data for **5**: R_f = 0.52 (EtOAc/petroleum ether, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.02 (d, H-1, $J_{1,2}$ = 3.0 Hz), 5.06 (d, H-2), 4.93 (brt, H-4), 4.28-4.18 (m, CH_2CH$_3$), 3.40 (br. d, part A of AB system, H-5a, $J_{5a,5b}$ = 12.6 Hz), 3.26 (d, part A of AB system, H-3'a, $J_{3a,3b}$ = 16.7 Hz), 3.18 (br. d, part B of AB system, H-5b), 2.80, 2.75 (d, part B of AB system, H-3'b), 1.53 (Me), 1.36 (Me), 1.29 (t, CH$_2$CH_3) ppm.

Data for **6**: R_f = 0.45 (EtOAc/petroleum ether, 1:9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.98 (d, H-1, $J_{1,2}$ = 5.3 Hz), 5.33 (d, H-2), 4.16 (qd, CH_2CH$_3$), 3.71 (d, part A of AB system, H-5a, $J_{5a,5b}$ = 14.4 Hz) 3.59 (d, part B of AB system, H-5b), 3.37 (d, part A of AB system, H-3'a, $J_{3a,3b}$ = 16.7 Hz), 3.18 (d, part B of AB system, H-3'b), 2.34 (s, Me, SAc), 1.44 (s, Me, isopr.), 1.36 (s, Me, isopr.), 1.31 (t, CH$_2$CH_3) ppm.

3-Deoxy-2-*O*,3-*C*-(1-oxoethan-1-yl-2-ylidene)-5-thio-D-*erythro*-pentopyranose (7): Ethyl (3*Z*)-(5-*S*-Acetyl-3-deoxy-1,2-*O*-isopropylidene-5-thio-α-D-erythro-pentofuranos-3-ylidene)acetate (**4**, 0.45 g, 1.43 mmol) was dissolved in MeOH/H_2O (20 mL , 1.5/1 v/v) and NaOH solution (10 M, 0.27 mL) was added. After the system had been stirred at room temp. for 15 min, Amberlite IR-120 H^+ was added until neutralization. The resin was then filtered off and the solvents were evaporated. The resulting residue was dissolved in aq. AcOH (70%, 18 mL) and the solution was stirred under reflux for 2 h. The solvent was co-evaporated with toluene and the crude product was purified by CC (EtOAc/petroleum ether, 2:3 then 3:2) to afford **7** (93 mg, 35%, two steps) as a colorless oil. R_f = 0.26 (EtOAc/petroleum ether, 3:2). $[\alpha]_D^{20}$ = +130 (c = 1.1, in MeOH). ^{1}H NMR (400 MHz, CD_3OD, α anomer): δ = 6.02 (t, H-3', $J_{3',4} = J_{2,3'}$ = 1.5 Hz), 5.26–5.22 (m, 2H, H-1, H-2), 4.68 (ddd, 1H, H-4, $J_{4,5a}$ = 6.1, $J_{4,5b}$ = 10.9 Hz), 2.92 (dd, part A of ABX system, H-5a, $J_{5a,5b}$ = 12.6 Hz), 2.78 (dd, part B of ABX system, H-5b) ppm. ^{13}C NMR (100 MHz, CD_3OD): δ = 174.8 (*C*O, lac), 171.9 (C-3), 115.5 (C-3'), 84.6 (C-2), 73.3 (C-1), 70.4 (C-4), 31.3 (C-5) ppm. HRMS: calcd. for $C_7H_8O_4S$ [*M* + Na]$^+$ 211.0036, found 211.0031.

1,4-Di-*O*-acetyl-3-deoxy-2-*O*,3-*C*-(1-oxoethan-1-yl-2-ylidene)-5-thio-D-*erythro*-pentopyranose (8) and 4-*O*-Acetyl-l,5-anhydro-3-deoxy-2-*O*,3-*C*-(1-oxoethan-1-yl-2-ylidene)-5-thio-D-*glycero*-pent-l-enitol (9): Ac_2O (0.35 mL) was added to a solution of 3-deoxy-2-*O*,3-*C*-(1-oxoethan-1-yl-2-ylidene)-5-thio-D-*erythro*-pentopyranose (**7**, 7 mg, 37 μmol) in py (0.7 mL), and the mixture was stirred at room temp. for 5 min. After coevaporation with toluene, the crude product was purified by CC (EtOAc/petroleum ether, 2:3) to afford **8** (8 mg, 80%) as a colorless oil and traces of the corresponding glycal **9**.

Data for **8**: R_f = 0.21 (EtOAc/petroleum ether, 2:3). $[\alpha]_D^{20}$ = +50 (c = 0.5, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.27 (d, H-1α, $J_{1,2(\alpha)}$ = 3.8 Hz), 6.08 (t, H-3'α) 6.07 (t, H-3'β, $J_{2,3'(\beta)} \sim J_{3',4(\beta)} \sim$ 1.8 Hz), 5.78 (dddd, 1H, H-4α), 5.69 (dddd, 1H, H-4β), 5.60 (d, H-1β, $J_{1,2(\beta)}$ = 9.1), 5.23 (ddd, 1H, H-2α), 5.13 (ddd, H-2β), 3.13 (dd, H-5aβ, $J_{4,5a(\beta)}$ = 5.3, $J_{5a,5b(\beta)}$ = 13.1) 3.01 (dd, part A of ABX system, H-5aα, $J_{4,5a(\alpha)}$ = 5.3, $J_{5a,5b(\alpha)}$ = 12.9 Hz), 2.91 (dd, part B of ABX system, H-5bα, $J_{4,5b(\alpha)}$ = 10.9 Hz), 2.73 (dd, H-5bβ, $J_{4,5b(\beta)}$ = 10.9 Hz), 2.21 (s, Meα, Ac), 2.08 (s, 3H, Meα, Ac) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major anomer): δ = 170.4 (*C*O), 169.4, 168.6 (*C*O, Ac), 162.3 (C-3), 116.4 (C-3'), 80.0

(C-2), 70.7 (C-1), 69.3 (C-4), 28.9 (C-5), 20.9 (Me, Ac), 20.8 (Me, Ac) ppm. HRMS: calcd. for $C_{11}H_{12}O_6S$ $[M + Na]^+$ 295.0247, found 295.0254.

Data for **9:** R_f = 0.53 (EtOAc/petroleum ether, 3:2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.47 (d, 1H, H-1, $^5J_{1,3'}$ = 1.5), 6.03 (t, 1H, H-3', $^5J_{1,3'} = {}^4J_{3',4}$ = 1.5 Hz), 5.97 (td, 1H, H-4, $J_{4,5a} = J_{4,5b}$ = 7.3), 3.16 (br. d, 2H, CH_2-5), 2.19 (s, 3H, Me, Ac) ppm. HRMS: calcd. for $C_9H_8O_4$ $[M + H]^+$ 213.0216, found 213.0223; calcd. for $[M + Na]^+$ 235.0036, found 235.0044.

Ethyl (3*Z*)-[(6-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ylidene]acetate (11): DMAP (16 mg, 0.13 mmol), and TBDMSCl (0.58 g, 3.85 mmol) were added at room temp. under argon to a solution of ethyl (3*Z*)-(3-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ylidene)acetate [16a] (**10**, 0.52 g, 1.8 mmol) in dry py (2 mL). After stirring for 15 h, the reaction mixture was poured into water (12 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water and brine and dried with anhydrous $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by CC (EtOAc/petroleum ether, 1:6) to afford **11** (0.632 g, 87%) as colorless oil. R_f = 0.33 (EtOAc/cyclohexane, 1:5). $[\alpha]_D^{20}$ = +111 (c = 1.2, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.44 (br. s, 1H, H-3'), 5.82 (d, 1H, H-1, $J_{1,2}$ = 3.8 Hz), 5.72 (br. d, 1H, H-2), 4.66 (br. d, 1H, H-4, $J_{4,5}$ = 7.6 Hz), 4.21 (q, 2H, CH_2CH_3, J = 7.1 Hz), 3.79–3.69 (m, H-6a, H-6b), 3.65–3.57 (m, 1H, H-5), 2.74 (d, 1H, OH-5, J = 6.1 Hz), 1.47 (s, 3H, Me, isopr.), 1.39 (s, 3H, Me, isopr.), 1,28 (t, 3H, CH_2CH_3), 0.88 (s, 9H, *t*Bu, TBDMS), 0.07 (2 × s, 6H, Me, TBDMS) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5 (*C*O), 156.3 (C-3), 117.6 (C-3'), 112.8 (Cq, isopr.), 104.9 (C-1), 78.9 (C-4), 78.4 (C-2), 73.2 (C-5), 63.8 (C-6), 60.7 (CH_2CH_3), 27.4 (Me, isopr.), 27.3 (Me, isopr.), 25.9 (3 × Me, *t*Bu), 18.4 (Cq, *t*Bu), 14.3 (CH_2CH_3), -5.3 (Me, TBDMS), -5.3 (Me, TBDMS) ppm. HRMS: calcd. for $C_{19}H_{34}O_7Si$ $[M + Na]^+$ 425.1966, found 425.1981.

Ethyl (3*Z*)-[(6-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-1,2-*O*-isopropylidene-5-*O*-mesyl-α-D-*ribo*-hexofuranos-3-ylidene]acetate (12): Methanesulfonyl chloride (0.03 mL, 0.43 mmol) was added under argon at 0 °C to a solution of ethyl (3*Z*)-[(6-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ylidene]-acetate (**11**, 0.116 g, 0.29 mmol) in dry py (2.9 mL). The ice bath was removed and the

solution was kept stirring at room temp. for 40 min. Water (12 mL) was added to the solution, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water and dried with anhydrous $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by CC (EtOAc/petroleum ether, 1:3) to afford **12** (0.131 g, 95%) as a colorless oil. R_f = 0.47 (EtOAc/petroleum ether, 1.5:3.5). $[\alpha]_D^{20}$ = +91 (c = 1.1, in CH_2Cl_2).^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.07 (t, 1H, H-3', $J_{2,3'} = J_{3',4}$ = 1.8 Hz), 5.89 (d, 1H, H-1, $J_{1,2}$ = 4.0 Hz), 5.69 (dt, 1H, H-2, $J_{2,3'} = J_{2,4}$), 5.15 (ddd, 1H, H-4), 4.71 (ddd, 1H, H-5), 4.23 (qd, 2H, C*H*$_2$CH$_3$, J = 7.1 Hz), 3.89 (dd, part A of ABX system, 1H, H-6a, $J_{5,6a}$ = 6.6, $J_{6a,6b}$ = 11.4 Hz), 3.80 (dd, part B of ABX system, 1H, H-6b, $J_{5,6b}$ = 5.8 Hz), 3.08 (s, 3H, Me, Ms), 2.26 (br. s, 1H, OH-6), 1.45 (s, 3H, Me, isopr.), 1.41 (s, 3H, Me, isopr.), 1.30 (t, 3H, CH$_2$C*H*$_3$), 0.87 (s, 9H, *t*Bu, TBDMS), 0.07 (s, 3H, Me, TBDMS), 0.06 (s, 3H, Me, TBDMS) ppm.^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.6 (*C*O), 153.7 (C-3), 118.6 (C-3'), 113.4 (Cq, isopr.), 105.6 (C-1), 82.7 (C-5), 79.8 (C-4), 78.8 (C-2), 61.4 (C-6), 60.9 (*C*H$_2$CH$_3$), 38.8 (Me, Ms), 27.6 (Me, isopr.), 27.4 (Me, isopr.), 25.9 (3 × Me, *t*Bu), 18.4 (Cq, *t*Bu), 14.2 (CH$_2$*C*H$_3$), 5.3 (Me, TBDMS), -5.4 (Me, TBDMS) ppm. HRMS: calcd. for $C_{20}H_{36}O_9SSi$ [*M* + Na]$^+$ 503.1742, found 503.1760.

Ethyl [3,5-Anhydro-6-*O*-(*tert*-butyldimethylsilyl)-1,2-*O*-isopropylidene-5-thio-β-L-*ido*-hexofuranos-3-*C*-yl]acetate (13) and Ethyl [5-*S*-acetyl-6-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-1,2-*O*-isopropylidene-5-thio-β-L-*threo*-hex-3-enofuranos-3-*C*-yl]acetate (14): Potassium thioacetate (36 mg, 0.31 mmol) was added under argon to a solution of ethyl (3*Z*)-[(6-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-1,2-*O*-isopropylidene-5-*O*-mesyl-α-D-*ribo*-hexofuranos-3-ylidene]acetate (**12**, 0.125g, 0.26 mmol) in anhydrous DMF (2.7 mL). The whole solution was stirred at 90 ºC for 24 h. Water was added (12 mL) and the organic phase was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with water and dried over $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by CC (EtOAc/ cyclohexane, 1:16) to afford **13** (12 mg, 15%) as a colorless oil, **14** (23 mg, 19%) and **15** (29 mg, 24%). Separation of **14** from **15** by chromatography was not possible.

Data for **13**. R_f = 0.47 (EtOAc/cyclohexane, 1:6). $[\alpha]_D^{20}$ = +14 (c = 0.5, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.03 (d, 1H, H-1, $J_{1,2}$ = 3.0 Hz), 5.04 (d, 1H, H-2), 4.73 (dd, 1H, H-4, $J_{4,5}$ = 1.3 Hz), 4.56 (dd, 1H, H-6a, $J_{5,6a}$ = 9.9, $J_{6a,6b}$ = 13.6 Hz), 4.25–4.15

(m, 2H, C*H*$_2$CH$_3$, *J* = 7.1), 3.86–3.78 (m, 2H, H-5, H-6b), 3.25 (d, part A of AB system, 1H, H-3'a, $J_{3'a,3'b}$ = 16.9 Hz), 2.78 (d, part B of AB system, 1H, H-3'b), 1.51 (s, 3H, Me, isopr.), 1.35 (s, 3H, Me, isopr.), 1.29 (t, 3H, CH$_2$C*H*$_3$), 0.89 (s, 9H, *t*-Bu, TBDMS), 0.07 (br. s, 6H, Me, TBDMS) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 113.3 (Cq, isopr.), 106.7 (C-1), 89.9 (C-4), 86.5 (C-2), 64.0 (C-5), 61.4, 61.3 (C-6, *C*H$_2$CH$_3$), 27.7 (Me, isopr.), 27.2 (Me, isopr.), 26.0 (3 × Me, *t*Bu), 18.4 (Cq, *t*Bu), 14.3 (CH$_2$*C*H$_3$), -5.4 (2×Me, TBDMS) ppm. HRMS: calcd. for $C_{19}H_{34}O_6SSi$ [*M* + Na]$^+$ 441.1738, found 441.1756.

Data for **14**. R_f = 0.37 (EtOAc/cyclohexane, 1:6). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.96 (d, 1H, H-1, $J_{1,2}$ = 5.3 Hz), 5.40 (d, 1H, H-2), 4.48 (dd, 1H, H-5, $J_{5,6a}$ = 7.8, $J_{5,6b}$ = 6.8 Hz), 4.17–4.10 (m, 2H, C*H*$_2$CH$_3$, *J* = 7.1 Hz), 3.83 (t, 1H, H-6a, $J_{6a,6b}$ = 10.1 Hz), 3.68 (dd, 1H, H-6b), 3.41 (d, part A of AB system, H-3'a, $J_{3'a,3'b}$ = 16.9 Hz), 3.14 (d, part B of AB system, 1H, H-3'b), 2.32 (s, 3H, Me, SAc), 1.44 (s, 3H, Me, isopr.), 1.35 (s, 3H, Me, isopr.), 1.27 (t, 3H, CH$_2$C*H*$_3$), 0.85 (s, 9H, *t*Bu, TBDMS), 0.04 (s, 3H, Me, TBDMS), 0.03 (s, 3H, Me, TBDMS) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.3 (*C*O, SAc), 170.8 (*C*O), 152.2 (C-4), 112.3 (Cq, isopr.), 106.6 (C-3), 104.5 (C-1), 85.3 (C-2), 62.7 (C-6), 60.9 (*C*H$_2$CH$_3$), 41.0 (C-5), 30.6 (Me, SAc), 29.9 (C-3'), 28.1 (2 × Me, isopr.), 25.9 (3 × Me, *t*Bu), 18.4 (Cq, *t*Bu), 14.3 (CH$_2$*C*H$_3$), -5.3 (Me, TBDMS), -5.4 (Me, TBDMS) ppm. HRMS: calcd. for $C_{21}H_{36}O_7SSi$ [*M* + Na]+ 483.1843, found 483.1875.

Ethyl (3*E*)-[5-*S*-Acetyl-6-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-1,2-*O*-isopropylidene-5-thio-β-L-*lyxo*-hexofuranos-3-ylidene]acetate (15) and Ethyl (3*Z*)-[6-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-5-*O*-formyl-1,2-*O*-isopropylidene-β-L-*lyxo*-hexofuranos-3-ylidene]acetate (17): A solution of ethyl (3*Z*)-[(6-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-1,2-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ylidene]-acetate (**11**, 0.241 g, 0.6 mmol) and dry py (0.1 mL, 1.2 mmol) in dry CH_2Cl_2 (3 mL) was cooled to −11 ºC (MeOH/ice bath) under argon. Tf_2O (0.11 mL, 0.66 mmol) was added dropwise and the reaction mixture was stirred for 15 min, whilst keeping the temperature below −5 ºC. The solution was diluted with EtOAc (10 mL) and sequentially washed with a satd. $NaHCO_3$ solution (5 mL) and aq. HCl solution (2 M, 5 mL). The aqueous layer was extracted twice with EtOAc and the combined organic phases were dried with anhydrous $MgSO_4$. After filtration and concentration to dryness,

the crude triflate **16** was used immediately for the next step without further purification. R_f = 0.53 (EtOAc/cyclohexane, 1:5).

Potassium thioacetate (75 mg, 0.66 mmol) was added to the crude triflate **16** in DMF (6 mL). The solution was stirred at room temp. for 40 min. Water (12 mL) was then added to the solution and it was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water and brine and dried with anhydrous $MgSO_4$. After filtration and evaporation under vacuum, the residue was purified by CC (EtOAc/ petroleum ether, 1:14) to afford **15** (70 mg, 25%) and **17** (15 mg, 6%) as colorless oils.

Data for **15**: R_f = 0.41 (EtOAc/petroleum ether, 1:5). $[\alpha]_D^{20}$ = +67 (c = 1.2, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86 (d, 1H, H-1, $J_{1,2}$ = 4.3 Hz), 5.83 (t, 1H, H-3', $J_{2,3'}$ = $J_{3',4}$ = 1.8 Hz), 5.70 (dt, 1H, H-2), 5.42–5.39 (m, 1H, H-4), 4.28–4.15 (m, 2H, C*H*$_2$CH$_3$, J = 7.1 Hz), 3.87 (ddd, 1H, H-5), 3.78 (t, 1H, H-6a, $J_{5,6a}$ = $J_{6a,6b}$ = 9.6 Hz), 3.67 (dd, 1H, H-6b, $J_{5,6b}$ = 5.6 Hz), 2.31 (s, 3H, Me, SAc), 1.47 (s, 3H, Me, isopr.), 1.42 (s, 3H, Me, isopr.), 1.30 (t, 3H, CH$_2$C*H*$_3$), 0.89 (s, 9H, *t*Bu, TBDMS), 0.09 (s, 3H, Me, TBDMS), 0.08 (s, 3H, Me, TBDMS) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.9 (*C*O, SAc), 165.1 (*C*O), 156.3 (C-3), 116.3 (C-3'), 113.0 (Cq, isopr.), 105.4 (C-1), 78.5, 78.2 (C-4, C-2), 63.0 (C-6), 60.9 (*C*H$_2$CH$_3$), 48.9 (C-5), 30.8 (Me, SAc), 27.5 (2 × Me, isopr.), 25.9 (3 × Me, *t*Bu), 18.4 (Cq, *t*Bu), 14.3 (CH$_2$*C*H$_3$), -5.2 (Me, TBDMS), -5.3 (Me, TBDMS) ppm. HRMS: calcd. for $C_{21}H_{36}O_7SSi$ [*M* + Na]$^+$ 483.1843, found 483.1856.

Data for **17**: R_f = 0.28 (EtOAc/petroleum ether, 1:5). $[\alpha]_D^{20}$ = +88 (c = 1.1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (s, 1H, OC*H*O), 5.95–5.91 (m, 2H, H-1, H-3', $J_{1,2}$ = 4.3, $J_{2,3'}$ = $J_{3',4}$ = 1.5 Hz), 5.69 (dt, 1H, H-2, $J_{2,3'}$ = $J_{2,4}$), 5.21 (td, 1H, H-5 $J_{5,6a}$ = $J_{5,6b}$ = 6.8 Hz), 5.14–5.12 (m, 1H, H-4), 4.28–4.18 (m, 2H, C*H*$_2$CH$_3$, J = 7.1 Hz), 3.87–3.77 (m, 1H, H-6a, H-6b, $J_{6a,6b}$ = 10.1 Hz), 1.48 (s, 3H, Me, isopr.), 1.44 (s, 3H, Me, isopr.), 1.30 (t, 3H, CH$_2$C*H*$_3$, J = 7.1 Hz), 0.88 (s, 9H, *t*Bu, TBDMS), 0.08 (s, 3H, Me, TBDMS), 0.08 (s, 3H, Me, TBDMS) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8 (*C*O, O*C*HO), 160.1 (*C*O), 154.7 (C-3), 117.4 (C-3'), 113.4 (Cq, isopr.), 105.6 (C-1), 78.6, 78.5 (C-4, C-2), 73.6 (C-5), 61.1, 61.0 (*C*H$_2$CH$_3$, C-6), 30.8 (Me, SAc), 27.7 (Me, isopr.), 27.4 (Me, isopr.), 25.9 (3 × Me, *t*Bu), 18.3 (Cq, *t*Bu), 14.2 (CH$_2$*C*H$_3$), -5.3 (Me, TBDMS), -5.3 (Me, TBDMS) ppm. HRMS: calcd. for $C_{17}H_{30}O_6SSi$ [*M* + Na]$^+$ 413.1915, found 453.1915; calcd. for [*M* + K]$^+$ 469.1655, found 469.1656.

(3*E*)-[6-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-1,2-*O*-isopropylidene-5-sulfanyl-β-L-*lyxo*-hexofuranos-3-ylidene]acetic acid (18): Ethyl (3*E*)-[5-*S*-acetyl-6-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-1,2-*O*-isopropylidene-5-thio-β-L-*lyxo*-hexofuranos-3-ylidene]acetate (**15**, 41 mg, 0.09 mmol) was dissolved in MeOH/H_2O (2:1, 1.3 mL), and NaOH solution (10 M, 0.04 mL) was added. The solution was stirred at room temp. for 1 h, and then neutralized with Amberlite IR-120 H^+. After filtration of the resin and evaporation of the solvent, the residue was purified by CC (EtOAc/petroleum ether, 1:1) to afford **18** (23 mg, 66%) as a colorless oil. R_f = 0.4 (EtOAc/petroleum ether, 1:1). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 6.00 (d, 1H, H-1, $J_{1,2}$ = 4.0 Hz), 5.97 (t, 1H, H-3', $J_{2,3'} = J_{3',4}$ = 1.5 Hz), 5.72 (dt, 1H, H-2, $J_{2,3'} = J_{2,4}$), 5.39–5.35 (m, 1H, H-4), 3.81 (dd, 1H, H-6a, $J_{5,6a}$ = 5.6, $J_{6a,6b}$ = 9.9 Hz), 3.71 (t, 1H, H-6b, $J_{5,6b} = J_{6a,6b}$), 3.21 (tdd, 1H, H-5), 1.71 (d, 1H, S*H*, $J_{SH,H-5}$ = 10.1 Hz), 1.40 (s, 3H, Me, isopr.), 1.34 (s, 3H, Me, isopr.), 0.92 (s, 9H, *t*Bu, TBDMS), 0.12 (s, 3H, Me, TBDMS), 0.12 (s, 3H, Me, TBDMS) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 166.1 (*C*OOH), 158.4 (C-3), 117.4 (C-3'), 112.9 (Cq, isopr.), 106.7 (C-1), 79.6, 79.5 (C-2, C-4), 66.5 (C-6), 46.0 (C-5), 27.7 (Me, isopr.), 27.6 (Me, isopr.), 26.2 (3 × Me, *t*Bu), 18.8 (Cq, *t*Bu), 14.3 (CH_2CH_3), -5.2 (Me, TBDMS), -5.3 (Me, TBDMS) ppm. HRMS: calcd. for $C_{17}H_{30}O_6SSi$ [*M* + Na]$^+$ 413.1425, found 413.1435; calcd. for [*M* + K]$^+$ 429.1164, found 429.1171.

3-Deoxy-[2-*O*,3-*C*-(1-oxoethan-1-yl-2-ylidene)]-5-thio-L-*lyxo*-hexopyranose (19): A solution of (3*E*)-[6-*O*-(*tert*-butyldimethylsilyl)-3-deoxy-1,2-*O*-isopropylidene-5-sulfanyl-β-L-*lyxo*-hexofuranos-3-ylidene]acetic acid (**18**, 18 mg, 46 μmol) in aq. TFA (60%, 1 mL) was stirred at 40 ºC for 20 min. The solvent was co-evaporated with toluene and the crude product was purified by CC (EtOAc) to afford **19** (10 mg, quantitative) as a colorless oil. R_f = 0.41 (EtOAc). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 6.02 (br. d, H-3'β, *J* = 1.5 Hz), 6.00 (1, H-3'α, *J* = 1.8 Hz), 5.22–5.16 (m, H-1α, H-1β, H-2α) 5.10–5.05 (m, H-4α, H-4β), 4.98 (dd, H-2β, $J_{1,2(\beta)}$ = 8.6 Hz), 4.31 (dd, H-6a, $J_{5,6a}$ = 3.5, $J_{6a,6b}$ = 11.6), 3.90 (d, CH_2-6, $J_{5,CH2\text{-}6}$ = 5.8 Hz), 3.72 (dd, H-6b, $J_{5,6b}$ = 4.3 Hz), 3.40 (ddd, H-5), 3.20 (q, H-5, $J_{5,CH2\text{-}6} = J_{4,5}$) ppm.^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 172.3, *C*O, lac), 170.7 (C-3), 116.1 (C-3'), 115.8 (C-3'), 86.3 (C-2β), 83.0, 76.6, 73.0 (C-2α, C-1α, C-1β), 71.6, 70.2 (C-4α, C-4β), 62.7, 62.1 (C-6α, C-6β), 50.3, 49.2 (C-5α, C-5β) ppm. HRMS: calcd. for $C_8H_{10}O_5S$ [*M* + Na]$^+$ 241.0141, found 241.0147; calcd. for [*M* + K]$^+$ 256.9881, found 256.9888.

1,4,6-Tri-*O*-acetyl-3-deoxy-[2-*O*,3-*C*-(1-oxoethan-1-yl-2-ylidene)]-5-thio-L-*lyxo*-hexopyranose (20) and 4,6-Di-*O*-acetyl-l,5-anhydro-3-deoxy-[2-*O*,3-*C*-(1-oxoethan-1-yl-2-ylidene)]-5-thio-L-*threo*-hex-l-enitol (21): Ac_2O (0.35 mL) was added to a solution of 3-deoxy-[2-*O*,3-*C*-(1-oxoethan-1-yl-2-ylidene)]-5-thio-L-*lyxo*-hexopyranose (**19**, 8 mg, 37 μmol) in py (0.7 mL), and the mixture was stirred at room temp. for 5 min. After co-evaporation with toluene, the crude product was purified by CC (EtOAc/petroleum ether, 1:4) to afford the thioglycal-fused butenolide **21** (8.5 mg, 82%) as colorless oil, together with traces of the triacetate derivative **20** (α/β ratio, 1:1).

Data for **20**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.27 (d, H-1α, $J_{1,2(\alpha)}$ = 4.5 Hz), 6.22 (br. s, H-3'α), 6.11–6.07 (m, H-1β, H-3'β), 6.04 (br. dd, H-4α, $J_{4,5a(\alpha)}$ = 6.1 Hz), 5.97 (br. dd, H-4β, $J_{4,5a(\beta)}$ = 6.6 Hz), 5.60 (d, H-1β, $J_{1,2(\beta)}$ = 9.1 Hz), 5.24 (br. d, H-2α), 5.17 (ddd, 2β-H , $J_{1,2(\beta)}$ = 8.6 Hz), 4.48–4.19 (m, H-6aα, H-6bα, H-6aβ, H-6bβ) 3.72 (ddd, H-5α), 3.58 (ddd, H-5β) , 2.22, 2.21, 2.17, 2.12, 2.07, 2.06 (3 × Me, Ac, α, 3 × Me, Ac, β) ppm. HRMS: calcd. for $C_{14}H_{16}O_8S$ $[M + Na]^+$ 367.0458, found 367.0467.

Data for **21**: R_f = 0.15 (EtOAc/petroleum ether, 1:4). $[\alpha]_D^{20}$ = +8 (c = 0.7, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.35 (d, 1H, H-1, $^5J_{1,3'}$ = 1.5 Hz), 6.16 (dd, 1H, H-4, $J_{3',4}$ = 1.3, $J_{4,5}$ = 4.0 Hz), 6.10 (t, 1H, H-3'), 4.40 (dd, 1H, H-6a, $J_{5,6a}$ = 5.3, $J_{6a,6b}$ = 11.6 Hz), 4.25 (dd, 1H, H-6b, $J_{5,6a}$ = 7.8 Hz), 3.67 (ddd, 1H, H-5), 2.20 (s, 3H, Me, Ac), 2.09 (s, 3H, Me, Ac) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5 (*C*O), 123.4 (C-2), 114.3 (C-3'), 106.2 (C-1), 66.6 (C-4), 60.7 (C-6), 43.6 (C-5), 20.8 (CH_3, Me, Ac) ppm. HRMS: calcd. for $C_{12}H_{12}O_6S$ $[M + H]^+$ 285.0427, found 285.0434; calcd. for $[M + Na]^+$ 307.0247, found 307.0254.

(3*R*)-1,2-*O*-Isopropylidene-α-D-*ribo*-hexos-3-ulo-1,4:3,6-difuranose (23): A similar protocol than that described in ref. [20] was used with slight modifications. A solution of 1,2;5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuranosid-3-ulose (**22**, 1.61 g, 6.23 mmol) in aq. AcOH (60%, 18 mL) was stirred at room temp. overnight. The solvent was co-evaporated with toluene (3×) and the residue was purified by CC (EtOAc), to afford **23** **(**1.25 g, 92%). Physical data were in agreement with those reported. ^{1}H NMR (400 MHz, $CDCl_3$): δ = ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.97 (d, 1H, H-1, $J_{1,2}$ = 3.8 Hz), 4.56–4.47 (m, 1H, H-5), 4.46–4-42 (m, 2H, H-2, OH-3), 4.31–4.22 (m, 2H, H-4, H-6a, $J_{5,6a}$ = 6.3, $J_{6a,6b}$ = 9.3 Hz), 3.78 (dd, 1H, H-6b, $J_{5,6b}$ = 5.6 Hz), 2.87 (d, 1H, OH-5, $J_{H\text{-}5,OH}$ = 6.1 Hz), 1.59 (s, 3H, Me, isopr.), 1.41 (s, 3H, Me, isopr.) ppm. ^{13}C NMR (100 MHz,

$CDCl_3$): δ = 114.1 (Cq, isopr.), 111.0 (C-3), 107.1 (C-1), 84.2 (C-2), 82.9 (C-4), 73.9 (C-6), 71.2 (C-5), 27.3 (Me, isopr.), 27.3 (Me, isopr.) ppm.

(3*R*)-1,2-*O*-Isopropylidene-5-*O*-tosyl-α-D-*ribo*-hexos-3-ulo-1,4:3,6-difuranose (24): *p*-Toluenesulfonyl chloride (0.107 g, 0.56 mmol) was added under argon to a solution of (3*R*)-1,2-*O*-isopropylidene-α-D-*ribo*-hexos-3-ulo-1,4:3,6-difuranose (**23**, 0.111 g, 0.51 mmol) in dry py (2 mL). The solution was kept stirring at room temp. for 40 h. Water (12 mL) was added to the solution, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with water and dried with anhydrous $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by CC (EtOAc/petroleum ether, 3:7) to afford **24** (65 mg, 34%) as a colorless oil. R_f = 0.35 (EtOAc/petroleum ether, 3:7). $[\alpha]_D^{20}$ = +39 (c = 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (d, 2H, H-a, Ts, J = 8.3 Hz), 7.36 (d, 2H, H-b, Ts), 5.93 (d, 1H, H-1, $J_{1,2}$ = 4.0 Hz), 5.03 (ddd, 1H, H-5), 4.36 (d, 1H, H-2), 4.33 (d, 1H, H-4, $J_{4,5}$ = 4.3 Hz), 4.25 (dd, 1H, H-6a, $J_{5,6a}$ = 7.1, $J_{6a,6b}$ = 9.3 Hz), 3.94 (dd, 1H, H-6b, $J_{5,6b}$ = 7.1 Hz), 2.46 (s, 3H, Me, Ts), 1.51 (s, 3H, Me, isopr.), 1.37 (s, 3H, Me, isopr.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.5 (Cq-a, Tos), 132.8 (Cq-b), 130.1 (CH-b, Tos), 128.2 (CH-a, Ts), 114.1 (Cq, isopr.), 110.8 (C-3), 107.1 (C-1), 82.6, 82.4 (C-2, C-4), 77.0 (C-5), 70.0 (C-6), 27.3 (Me, isopr.), 27.2 (Me, isopr.), 21.8 (Me, Ts) ppm. HRMS: calcd. for $C_{16}H_{20}O_8S$ $[M + Na]^+$ 395.0771, found 395.0785.

(3*R*)-5-*S*-Acetyl-1,2-*O*-isopropylidene-5-thio-β-L-*lyxo*-hexos-3-ulo-1,4:3,6-difuranose (26). A solution of (3*R*)-1,2-*O*-isopropylidene-α-D-*ribo*-hexos-3-ulo-1,4:3,6-difuranose (**23**, 0.347 g, 1.59 mmol) and dry py (0.29 mL, 3.6 mmol) in dry dichloromethane (8 mL) was cooled to –11 ºC (MeOH/ice bath) under argon. Trifluoromethanosufonic anhydride (0.29 mL, 1.75 mmol) was added dropwise and the reaction was stirred whilst the temperature was kept below –5 ºC. After 10 min, TLC showed total consumption of **23**, and EtOAc (25 mL) was added. The solution was then washed with a sat. $NaHCO_3$ solution (12 mL) and aq. HCl solution (2 M, 12 mL). The aqueous layer was extracted twice with EtOAc and the combined organic phases were dried with anhydrous $MgSO_4$. After filtration and concentration to dryness, the crude triflate **25** was used immediately for the next step without further purification. R_f = 0.76 (EtOAc/petroleum ether, 2:3) [R_f (**23**) = 0.15 (EtOAc/petroleum ether, 2:3)].

Potassium thioacetate (0.2 g, 1.75 mmol) was added to the crude triflate **25** in DMF (15 mL). The solution was stirred at room temp. for 1 h 15 min. Water (30 mL) was then added to the solution, and it was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water and brine and dried with anhydrous $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by column chromatography (EtOAc/cyclohexane, 1:5) to afford **26** (0.205 g, 47%) as a white solid. R_f = 0.35 (EtOAc/petroleum ether, 1.5:3.5). m.p. 68.8–69.9 ºC. $[\alpha]_D^{20}$ = +36 (c = 1.0, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91 (d, 1H, H-1, $J_{1,2}$ = 4.3 Hz), 4.57–4.49 (m, 1H, H-6a), 4.42 (d, 1H, H-2), 4.41 (s, 1H, H-4), 4.12-4.05 (m, 2H, H-5, H-6b), 3.75 (s, 1H, OH) 2.37 (s, 3H, Me, SAc), 1.57 (s, 3H, Me, isopr.), 1.38 (s, 3H, Me, isopr.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.6 (*C*O, SAc), 117.1 (C-3'), 113.5 (Cq, isopr.), 111.8 (C-3), 106.2 (C-1), 88.8 (C-4), 81.3 (C-2), 75.2 (C-6), 44.8 (C-5), 30.6 (Me, SAc), 27.3 (Me, isopr.), 27.3 (Me, isopr.) ppm. HRMS: calcd. for $C_{11}H_{16}O_6S$ [*M* + Na]$^+$ 299.0560, found 299.0567; calcd. for [*M* + K]$^+$ 315.0299, found 315.0310.

(3*R*)-1,2-*O*-Isopropylidene-5-sulfanyl-β-L-*lyxo*-hexos-3-ulo-1,4:3,6-difuranose (27): (3*R*)-5-*S*-Acetyl-1,2-*O*-isopropylidene-5-thio-β-L-*lyxo*-hexos-3-ulo-1,4:3,6-difuranose (**26**, 50 mg, 0.18 mmol) was dissolved in MeOH/H_2O (2/1, 2.6 mL) and NaOH solution (10 M, 0.02 mL) was added. After the system had been stirred at room temp. for 5 min, TLC showed total conversion of **27**. The solution was then neutralized with Amberlite IR-120 H^+, the resin was filtered off and the solvent was evaporated. The residue was purified by column chromatography (EtOAc/cyclohexane, 1:5) to afford **27** (37.5 mg, 90%) as a white solid. R_f = 0.5 (EtOAc/petroleum ether, 1.5:3.5). m.p. 64.4–66.3 ºC. $[\alpha]_D^{20}$ = +22 (c = 1.2, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84 (d, 1H, H-1, $J_{1,2}$ = 4.0 Hz), 4.49 (s, 1H, H-4), 4.48–4-40 (m, 2H, H-2, H-6a, $J_{5,6a}$ = 6.3, $J_{6a,6b}$ = 9.3 Hz), 4.15 (dd, 1H, H-6b, $J_{5,6b}$ = 3.0 Hz), 3.83 (s, 1H, OH-3), 3.39 (ddd, 1H, H-5), 2.24 (d, 1H, SH, $J_{SH,5}$ = 9.6 Hz), 1.59 (s, 3H, Me, isopr.), 1.39 (s, 3H, Me, isopr.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 113.5 (Cq, isopr.), 112.1 (C-3), 105.8 (C-1), 91.0 (C-2), 81.8 (C-4), 77.8 (C-6), 40.4 (C-5), 27.3 (Me, isopr.), 27.3 (Me, isopr.) ppm. HRMS: calcd. for $C_9H_{14}O_5S$ [*M* + Na]$^+$ 257.0454, found 257.0456.

5-Thio-L-*lyxo*-hexopyran-3-ulose (28): A solution of (3*R*)-1,2-*O*-isopropylidene-5-sulfanyl-β-L-*lyxo*-hexos-3-ulo-1,4:3,6-difuranose (**27**, 22 mg, 94 μmol) in aq. TFA

(60%, 1 mL) was stirred at 40 ºC for 20 min. The solvent was co-evaporated with toluene and the crude product was purified by CC (EtOAc) to afford **28** (18 mg, quantitative) as a colorless oil. R_f = 0.22 (EtOAc). $[\alpha]_D^{20}$ = +23 (c = 1.2, in MeOH). ^{1}H NMR (400 MHz, CD_3OD): δ = 5.31 (d, H-1β, $J_{1,2(\beta)}$ = 8.6 Hz), 5.14 (d, 1H, H-1α, $J_{1,2(\alpha)}$ = 4.0 Hz), 4.79 (dd, 1H, H-4α, $J_{2,4(\alpha)}$ = 1.0, $J_{4,5(\alpha)}$ = 6.8 Hz), 4.68–4.63 (m, H-2α, H-4β), 4.31 (dd, H-2β, $J_{2,4(\beta)}$ = 1.0 Hz), 4.16 (dd, H-6aα, $J_{5,6a(\alpha)}$ = 4.0, $J_{6a,6b(\alpha)}$ = 11.1 Hz), 4.01 (dd, H-6aβ, $J_{5,6a(\beta)}$ = 4.0, $J_{6a,6b(\beta)}$ = 11.1 Hz), 3.72 (dd, H-6bβ, $J_{5,6b(\beta)}$ = 2.8 Hz), 3.62 (dd, H-6bα, $J_{5,6b(\alpha)}$ = 2.8 Hz), 3.52 (ddd, 1H, H-5α), 3.11 (ddd, H-5β) ppm. ^{13}C NMR (100 MHz, CD_3OD, major anomer): δ = 207.7 (*C*O), 79.5 (C-2α), 79.3 (C-1α), 76.5 (C-4α), 62.2 (C-6α), 52.4 (C-5α) ppm. HRMS: calcd. for $C_8H_{10}O_5S$ $[M + Na]^+$ 217.0141, found 217.0143; calcd. for $[M + K]^+$ 232.9881, found 232.9883.

2,4,6-Tri-*O*-acetyl-l,5-anhydro-5-thio-L-*threo*-hex-l-enopyran-3-ulose (29): Ac_2O (0.35 mL) was added to a solution of 5-thio-L-*lyxo*-hexopyranos-3-ulose (**28**, 11 mg, 57 μmol) in py (0.7 mL), and the mixture was stirred at room temp. for 5 min. After co-evaporation with toluene, the crude product was purified by CC (EtOAc/petroleum ether, 2:3) to afford **29** (16 mg, 94%) as a colorless oil. R_f = 0.52 (EtOAc/petroleum ether, 2:3). $[\alpha]_D^{20}$ = –6 (c = 0.2, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (d, H-1, $^6J_{1,5}$ = 1.5 Hz), 5.97 (d, 1H, H-4, $J_{4,5}$ = 5.1 Hz), 4.50–4.45 (m, 2H, H-6a, H-6b), 3.66 (dddd, 1H, H-5), 2.22 (s, 3H, Me, Ac-2), 2.21 (s, 3H, Me, Ac-4), 2.08 (s, 3H, Me, Ac-6) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 182.5 (*C*O), 170.6, 169.3, 168.6 (3 × *C*O, Ac), 138.6 (C-2), 130.6 (C-1), 73.0 (C-4), 60.8 (C-6), 43.6 (C-5), 20.8, 20.6, 20.3 (3 × Me, Ac) ppm. HRMS: calcd. for $C_{12}H_{14}O_7S$ $[M + Na]^+$ 325.0352, found 325.0346.

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2.3. Nitrogen-Containing Carbohydrate Derivatives Embodying an α,β-Unsaturated Carbonyl Functionality

This subchapter includes the paper:

"Exploitation of Furanoid 5-Azido-3-*C*-Branched-Chain Sugars Towards Highly Functionalized Nitrogen-Containing Carbohydrate Derivatives", Xavier, N. M.; Queneau, Y.; Rauter, A. P. *Eur. J. Org. Chem.* **2010**, in press.

and reports on the synthesis of functionalized amides comprising an α,β-unsaturated carbonyl function and on that of a 1,2-dihydropyridin-3-one starting from furanoid δ-amino α,β-unsaturated esters. This work also revealed interesting aspects about the reactivity of the furanoid 5-amino 3-*C*-α,β-unsaturated ester precursors when compared to that of the corresponding 5-*O*- and 5-*S*-analogues, which gave, under similar reaction conditions, bicyclic compounds possessing a butenolide fused to the sugar or the thiosugar moiety.

Eur. J. Org. Chem. **2010**, in press

Exploitation of Furanoid 5-Azido-3-*C*-Branched-Chain Sugars Towards Highly Functionalized Nitrogen-Containing Carbohydrate Derivatives

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Keywords: Imino sugar / Sugar amide / Butenolide / 1,2-Dihydropyridin-3-one / Ring expansion / Cyclization

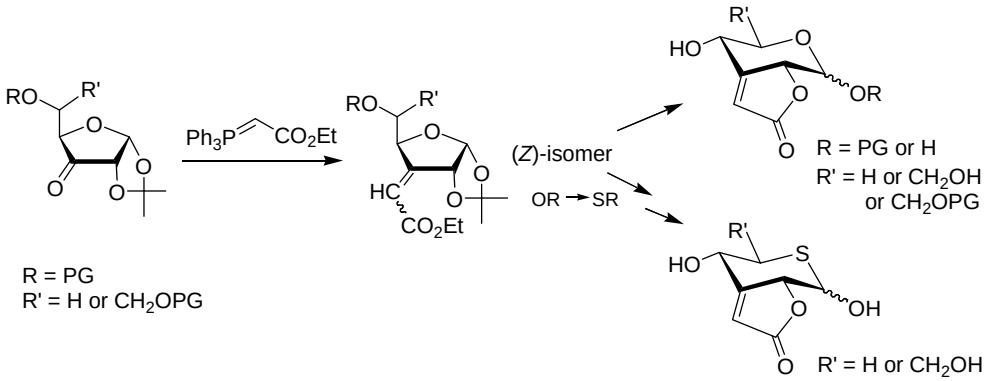
Abstract

The capability of easily accessed 5-azido-3-*C*-(ethoxycarbonyl)methylene-1,2-*O*-protected furanoses to serve as precursors for the generation of imino sugar derivatives containing an α,β-unsaturated lactone or an α,β-unsaturated ketone functionality, was investigated. A key aspect was the propensity of the corresponding deprotected δ-amino α,β-unsaturated esters to undergo 5-aminofuranose/iminopyranose isomerization. The δ-amino (*Z*)-α,β-unsaturated ester, when submitted to acid hydrolysis followed by treatment with base, led to a butenolide-containing *N*-ethylformamide, arising from the rearrangement of the imino sugar-fused butenolide intermediate, induced by the conjugated system. When carrying out the ring expansion step under neutral conditions, a 2-keto imino sugar was obtained, which was readily converted into a 1,2-dihydropyridin-3-one by acetylation. Furthermore, reduction of the δ-azido (*E*)-α,β-unsaturated ester to the amine was followed by spontaneous intramolecular cyclization, providing the related furanose-fused unsaturated δ-lactam.

Introduction

Imino sugars, in which the endocyclic oxygen atom of the sugar has been replaced by a nitrogen atom, constitute one of the most interesting classes of carbohydrate mimics, owing to their biological activities and therapeutic potential [1]. Probably the most intensively studied property of imino sugars is their aptitude to inhibit glycosidases by mimicking the natural substrates [1, 2]. Among such inhibitors are the naturally occurring nojirimycin and related compounds, including 1-deoxynojirimycin or 1-deoxymannojirimycin [2a]. First reports on the synthesis of imino sugars came out during mid-1960's [3] and since then a variety of methods have been developed, starting either from commercially available sugars or from non-carbohydrate precursors [4]. Methods using carbohydrate starting materials frequently rely on the introduction of a nitrogen function (azide or amine) and subsequent intramolecular cyclization by amino group attack to a carbonyl group, to a carbon adjacent to a leaving group or to an activated double bond.

As the search for original imino sugar structures remains a topic of biological and synthetic interest, we were motivated to exploit the access to novel imino sugar derivatives bearing α,β-unsaturated carbonyl functions. Such conjugated systems are considered to be essential for the bioactivity expression of many compounds due to their propensity to undergo Michael-type addition of enzymes' nucleophilic residues [5]. The inclusion of these functionalities in carbohydrates has provided advantageous scaffolds for derivatization and bioactive substances as well [6]. Particularly, some furanose C-C-linked α,β-unsaturated γ-lactones were described as antifungal [7] and potent insecticidal agents [8]. This biological profile has prompted the acquisition of pyranose-fused butenolides [9] and related thiosugar hybrid molecules [10]. These bicyclic compounds were synthesized by a strategy involving Wittig olefination of appropriately protected pento- or hexofuranos-3-ulose derivatives and subsequent acid hydrolysis of the intermediate furanose-3-*C*-branched α,β-unsaturated esters (Scheme 1). Within this latter step, cleavage of the protecting groups occurred with concomitant intramolecular lactonization and furanose to pyranose ring expansion. Introduction of additional sulphydryl functionality at C-5 of the intermediate α,β-unsaturated esters followed by deprotection, led to thiosugar analogues.



Scheme 1. Synthetic approach for butenolides fused to pento- or hexopyranoses and thiosugar analogues starting from furanos-3-uloses.

In this context, the aim of this work was to investigate the approach Wittig olefination/intramolecular cyclization for the synthesis of new functionalized molecules in which an α,β-unsaturated carbonyl system is embodied in an imino sugar core. For that purpose, furanoid 3-*C*-(ethoxycarbonyl)methylene-5-azido sugars were explored as key intermediates.

The target compounds are intended to serve as precursors for the synthesis of highly functionalized nitrogen-containing sugars and as potential bioactive agents with functions of biological profile combined in a single molecule.

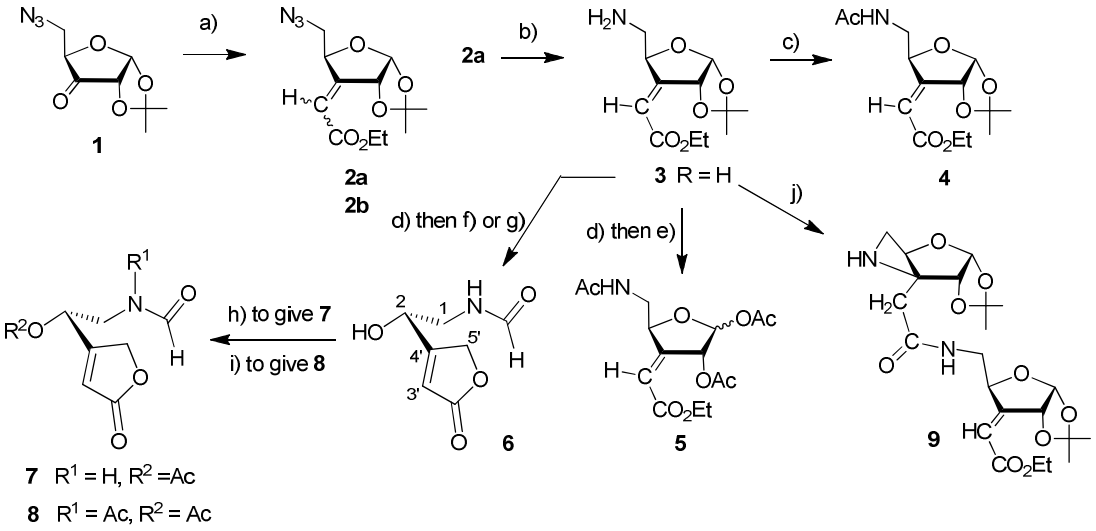
Results and Discussion

1. Iminopyranose-Fused Butenolide Acting as Intermediate for an Amide Functionalized Butenolide

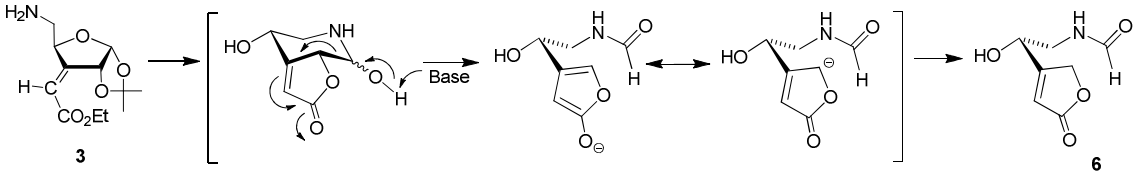
Synthesis of the suitable furanose precursors, carrying both the 5-nitrogen function and the exocyclic α,β-unsaturated ester moiety, started with 5-azido-pentofuranos-3-ulose **1** (Scheme 2) which was prepared by PDC/Ac_2O oxidation of 5-azido-5-deoxy-1,2-*O*-isopropylidene-α-D-pentofuranose [11], as previously reported [12]. Wittig-type olefination of **1** with [(ethoxycarbonyl)methylene]triphenylphosphorane in chloroform was completed within 30 min at room temp. to afford the (*Z*)- and (*E*)-α,β-unsaturated esters **2a**,**b** in 74% yield and 13% yield, respectively. Subsequent Staudinger reduction

of the azide group in **2a** with triphenylphosphane in the presence of H_2O gave the furanoid δ-amino α,β-unsaturated ester **3** in 84% yield, which was acetylated with Ac_2O in pyridine to the corresponding amide **4**. Having a free amine at C-5, we proceeded to the removal of the 1,2-*O*-isopropylidene group towards the formation of the iminopyranose ring. Treatment of **3** with aq. TFA (60%) at room temp. for 10 min was sufficient to achieve acetonide cleavage, as judged by TLC. After co-evaporation of the acid with toluene, the crude was immediately acetylated (Ac_2O/py) to afford **5** in 80% overall yield. Since no ring expansion was possible under these conditions, likely due to the protonation of the amine, an alternative work-up was performed. Hence, evaporation of the aq. TFA solution was followed by dissolution of the residue in EtOH-water, which was then treated with base, namely aq. NaOH solution or triethylamine, until pH 8 or 10 was reached, respectively. A single product was obtained, independently of the base used, and identified by NMR and HRMS as the butenolide-containing *N*-ethylformamide derivative **6**. In the ^{1}H NMR spectrum the singlet at δ 8.16 was indicative of a formyl proton and the HMBC correlation between this signal and C-1, which appeared at rather low chemical shift value (δ = 43.4 ppm), was in accordance with the presence of an amide group. The butenolide methylene protons (C*H*$_2$-5') were detected as a multiplet at δ 4.97–4.93 ppm, showing a weak coupling with H-3', while the signal for C-5 appeared at δ 71.8 ppm. The resonances of the carbonyl carbon atoms were observed at δ = 173.7 ppm and at δ = 172.4 ppm, corresponding to the butenolide moiety and to the *N*-formyl group, respectively. Selective *O*-acetylation of **6** with Ac_2O/py was achieved in 30 min affording **7** in 90% yield, while the addition of 4-dimethylaminopyridine (DMAP) in catalytic amount led to the product of further *N*-acetylation **8** in 84% yield. Mechanistically, the formation of **6** is thought to proceed via the iminopentopyranose-fused butenolide intermediate, which in basic medium is deprotonated at the anomeric hydroxyl group. The formed enolate-type anion, stabilized by resonance, then undergoes protonation at C-5' (Scheme 3). Addition of base is thus necessary to neutralize excess of acid, releasing the amine group for cyclization. However its use in the presence of the α,β-unsaturated carbonyl moiety induced the rearrangement of the target bicyclic compound to derivative **6.**

It is also worthy mention the potential use of furanoid δ-amino ester **3** as monomer for the generation of amide-linked oligomers. After storage for 1 month in a refrigerator (5 ºC), ca. 50% of **3** spontaneously evolved towards the amide-linked disaccharide **9**, arising from intramolecular Michael addition and intermolecular amide bond formation.



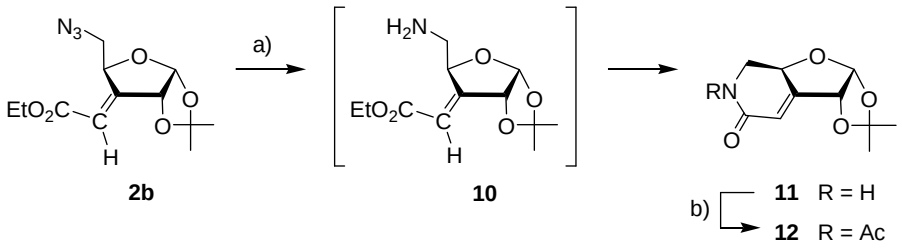
Scheme 2. Reactions and conditions: a) $Ph_3P{=}CHCO_2Et$, $CHCl_3$, room temp., 30 min; 74% (**2a**) and 13% (**2b**); b) PPh_3, H_2O/THF, room temp., 16 h, 84%; c) Ac_2O, py, room temp., 5 min, 90%; d) TFA 60% aq., room temp., 10 min; e) Ac_2O, py, room temp., 5 min, 80%, 2 steps; f) NaOH 1M, EtOH/H_2O, until pH 8, 45%, 2 steps; g) NEt_3, EtOH/H_2O until pH 10, 65%, 2 steps; h) Ac_2O, py, room temp., 30 min, 90%; i) Ac_2O, catalytic DMAP, py, room temp., 1 h, 84%; j) storage at 5 ºC, 1 month, 50%.



Scheme 3. Plausible mechanism for the formation of compound **6**.

2. Synthesis of a Furanose-Fused α,β-Unsaturated-δ-Lactam

In contrast with the amine **3**, the furanoid δ-amino-(*E*)-α,β-unsaturated ester **10**, resulting from Staudinger reduction of the (*E)*-azido precursor **2b**, could not be isolated and was obtained together with the furanose-fused δ-lactam **11** (Scheme 4). The intramolecular amidation of **10** was shown to be spontaneous and a clean conversion to **11** (89% overall yield) was attained simply by letting the referred mixture stand overnight in solution. DMAP-catalysed acetylation of **11** furnished the corresponding *N*-acetyl lactam derivative **12** in 85% yield.



2b

Scheme 4. Reactions and conditions: a) PPh_3, H_2O/THF, room temp., 16 h to give **10** and **11** (ratio 0.35/1), then CH_2Cl_2, 16 h, 89% (**11**); b) Ac_2O, catalytic DMAP, py, room temp., 16 h., 85%.

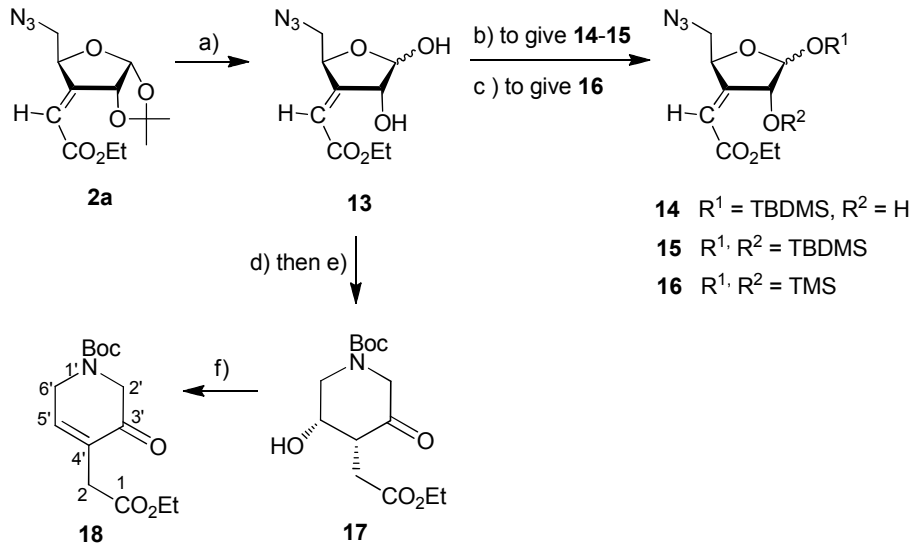
3. Synthesis of 1,2-Dihydropyridin-3-one

Hydrolysis of the 1,2-*O*-isopropylidene group of **2a** prior to azide reduction was figured to be a feasible alternative to the strategy depicted in Scheme 2, in order to allow the furanose to 5-aminofuranose/iminopyranose isomerization to occur under neutral conditions (Scheme 5). Hence, TFA-promoted hydrolysis of **2a** gave the 1,2-diol **13** in 94% yield. No intermolecular transesterification leading to the furanose-fused butenolide was observed, in accordance with the previously reported results for similar furanoid γ-hydroxy α,β-unsaturated carbonyl systems [9a]. Staudinger reduction was subsequently attempted, however leading to decomposition of diol **13**. In order to check whether this result would be different with protection of the 1,2-hydroxyl groups, silylation of **13** was carried out. Silyl ethers can be cleaved by TBAF and, regarding the conditions required for the access to the target bicyclic compound, their use as protecting groups may be advantageous to the acetonide functionality. Treatment of diol

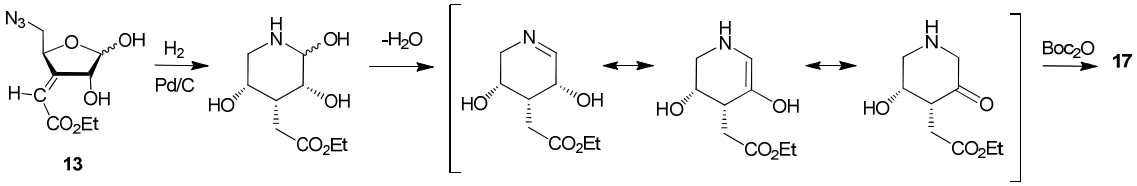
13 with *tert*-butyldimethylsilyl chloride (TBDMSCl) and a catalytic amount of DMAP in pyridine (15 h) afforded the monoprotected derivative **14** as the major product (55%), together with the 1,2-di-*O*-silyl derivative **15** (14%). On the other hand, as expected, reaction of **13** with trimethylsilyl chloride (TMSCl) in the presence of triethylamine and DMAP gave only the disilylated compound **16**. The ensuing experiments to selectively reduce the azide group of compounds **14** and **16** using the Staudinger method were not successful and only decomposition of the starting materials was observed by TLC. Instead, hydrogenation of **13** was performed. Exposure of **13** to hydrogen atmosphere in the presence of 10% Pd/C was followed by addition of *tert*-butoxycarbonyl anhydride (Boc_2O) to give keto iminosugar **17,** which upon acetylation (Ac_2O/py) resulted in the 1,2-dihydropyridin-3-one **18**. The structure of **18** was readily established by NMR. The ^{13}C NMR spectrum showed the signal of the carbonyl group at δ 192.5 ppm, which is typical of an α,β-unsaturated ketone. The olefinic proton (H-5') was observed at δ 6.92 ppm as a broad singlet and COSY experiments showed a weak coupling with the C-6' protons.

The formation of compound **17** is not surprising since imino sugars possessing an anomeric hydroxyl group are prone to dehydration due to the low stability of the hemiaminal function [13]. The resulting imine then isomerizes to the enol which in turn tautomerizes to the keto form, as shown in Scheme 6. Acetylation of **17** occurred with concomitant elimination of acetic acid to give the unsaturated enone system, which is consistent with the known tendency of β-acylated pyranuloses for α,β-elimination [14].

1,2-Dihydropyridin-3-ones are generally obtained in low global yield by methodologies usually requiring various synthetic steps [15, 16]. Our approach provided compound **18** after 5 steps and in 29% overall yield starting from the readily prepared 5-azido-3-ulose **1**. This molecule is structurally suitable to be a useful synthon for new imino sugar derivatives. Enones of this family have been used as key intermediates for the synthesis of natural products [15, 17], including 1-deoxynojirimycin [17a], deoxymannojirimycin and deoxygulonojirimycin [15].



Scheme 5. Reactions and conditions: TFA 60% aq., room temp., 5 min, 94%; b) TBDMSCl, py, catalytic DMAP, room temp., 15 h, 55% (**14**) and 14% (**15**); c) TMSCl, NEt_3, catalytic DMAP, CH_2Cl_2, room temp., 10 min, 67%; d) H_2, 10% Pd/C, EtOH, room temp., 40 min; e) Boc_2O, room temp., 1 h 30 min; f) Ac_2O/py, room temp., 30 min, 42%, 3 steps.



Scheme 6. Generation of 2-keto imino sugar **17** by hydrogenation (H_2, 10% Pd/C, EtOH, room temp., 40 min) of furanoid δ-azido-(Z)-α,β-unsaturated ester 13.

Conclusions

Furanoid (*Z*)- and (*E*)-3-*C*-(ethoxycarbonyl)methylene 5-azido sugars proved to be useful precursors for the acquisition of carbohydrate or non-carbohydrate molecules comprising an α,β-unsaturated lactone or an α,β-unsaturated ketone functionality, by reliable approaches involving few synthetic steps. The corresponding (*E*)- and (Z)-δ-amino α,β-unsaturated esters were converted, through intramolecular cyclization, to a furanose-fused α,β-unsaturated δ-lactam or to a butenolide-containing *N*-

ethylformamide, respectively. The ring expansion of 5-aminofuranose to iminopyranose was shown to be the dependent of the pH. A basic-medium mediated the rearrangement of the imino sugar-fused butenolide intermediate to a *N*-ethylformamide derivative, elicited by the conjugated carbonyl functionality. On the other hand, under neutral conditions, a 2-keto imino sugar was obtained, which was subsequently converted into a 1,2-dihydropyridin-3-one by acetylation. The α,β-unsaturated ester moiety also induced the spontaneous intermolecular amidation of the δ-amino (*Z*)-α,β-unsaturated ester along with concomitant Michael addition to give a pseudo dissacharide.

The newly accessed final compounds may be regarded as structurally interesting synthons for derivatization and novel candidates for bioactivity expression.

Experimental Section

General Methods: All reactions were followed by TLC on Merck 60 F_{254} silica gel aluminium plates with detection under UV light (254 nm) and/or by spraying with a solution of 10% H_2SO_4 in EtOH or with the Hanessian stain. Column chromatography (CC) was performed on silica gel 60 (0.040–0.063 mm, Merck). ^{1}H and ^{13}C NMR spectra were acquired with a Bruker Avance 400 spectrometer, operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C. Chemical shifts are expressed in parts per million and are referenced to solvent residual peaks. Assignments were made by COSY, HMQC, and by HMBC experiments. HRMS spectra were acquired in an Apex Ultra FTICR Mass Spectrometer equipped with an Apollo II Dual ESI/MALDI ion source, from Bruker Daltonics, and a 7T actively shielded magnet from Magnex Scientific. Optical rotations were measured on a Perkin–Elmer 343 polarimeter at 20 ºC (589 nm, sodium D line).

Ethyl (3*Z*)-(5-Azido-3,5-dideoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ylidene)acetate (2a) and Ethyl (3*E*)-(5-Azido-3,5-dideoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ylidene)acetate (2b): To a solution of the 3-ulose **1** [12] (0.2 g, 0.94 mmol) in dry $CHCl_3$ (8 mL) was added [(ethoxycarbonyl)-methylene]triphenylphosphorane (0.47 g, 1.35 mmol). The mixture was stirred at room temp. for 30 min. After evaporation of the solvent, the residue was purified by CC (EtOAc/petroleum ether, 1:8 then 1:6) to afford the (*Z*)-adduct **2a** (0.197 g, 74%) and its (*E*)-isomer **2b** (0.034 g, 13%) as colorless oils.

Data for **2a**: R_f = 0.27 (EtOAc/petroleum ether, 1:6). $[\alpha]_D^{20}$ = +224 (c = 1.1, in CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.91 (d, 1H, H-1, $J_{1,2}$ = 4.0 Hz), 5.82 (t, 1H, H-3', $J_{2,3'}$ = $J_{3',4}$ = 1.8 Hz), 5.71 (dt, 1H, H-2, $J_{2,3'}$ = $J_{2,4}$), 4.98–4.93 (m, 1H, H-4), 4.20 (q, 2H, CH_2CH$_3$, J = 7.1 Hz), 3.61 (dd, part A of ABX system, 1H, H-5a, $J_{4,5a}$ = 3.5, $J_{5a,5b}$ = 13.4 Hz), 3.36 (dd, part B of ABX system, 1H, H-5b, $J_{4,5b}$ = 4.2 Hz), 1.45 (s, 3H, Me, isopr.), 1.38 (s, 3H, Me, isopr.), 1.27 (t, 3H, CH$_2$CH_3) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 164.5 (*C*O), 154.6 (C-3), 117.2 (C-3'), 113.0 (Cq, isopr.), 105.0 (C-1), 78.8 (C-4), 78.2 (C-2), 60.9 (*C*H$_2$CH$_3$), 52.7 (C-5), 27.4 (Me, isopr.), 27.1 (Me isopr.), 14.1 (CH$_2$*C*H$_3$). HRMS: calcd. for $C_{12}H_{17}N_3O_5$ [M + Na]$^+$ 306.1060, found 306.1063.

Data for **2b**: R_f = 0.35 (EtOAc/petroleum ether, 1:8). $[\alpha]_D^{20}$ = +229 (c = 1.1, in CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.18 (t, 1H, H-3', $J_{2,3'}$ = $J_{3',4}$ = 1.8 Hz), 5.96 (d, 1H, H-1, $J_{1,2}$ = 4.5 Hz), 5.65–5.61 (m, 1H, H-4), 5.11 (dt, 1H, H-2, $J_{2,3'}$ = $J_{2,4}$), 4.18 (qd, 2H, CH_2CH$_3$), 3.71 (dd, part A of ABX system, 1H, H-5a, $J_{4,5a}$ = 2.8, $J_{5a,5b}$ = 12.9 Hz), 3.62 (dd, part B of ABX system, 1H, H-5b, $J_{4,5b}$ = 3.0 Hz) 1.41 (s, 3H, Me, isopr.), 1.38 (3H, Me, isopr.), 1.29 (t, 3H, CH$_2$CH_3, J = 7.1 Hz) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 165.4 (*C*O), 159.2 (C-3), 118.1 (C-3'), 113.4 (Cq, isopr.), 104.3 (C-1), 81.8 (C-2), 80.5 (C-4), 60.9 (*C*H$_2$CH$_3$), 54.9 (C-5), 27.9 (Me, isopr.), 27.8 (Me, isopr.), 14.2 (CH$_2$*C*H$_3$); HRMS: calcd. for $C_{12}H_{17}N_3O_5$ [M + H]$^+$ 284.1241, found 284.1239; calcd for [M + Na]$^+$ 306.1060, found 306.1062.

Ethyl (3*Z*)-(5-Amino-3,5-dideoxy-1,2-*O*-isopropylidene-*α*-D-*erythro*-pentofuranos-3-ylidene)acetate (3): A mixture of compound **2a** (0.075 mg, 0.27 mmol) and triphenylphosphine (0.136 g, 0.52 mmol) in H_2O (0.2 mL) and THF (2.6 mL) was stirred at room temp. for 16 h. After evaporation of the solvents, the residue was purified by CC (EtOAc then EtOAc/methanol, 6:1) to afford the title compound (0.057 g, 84%) as a colorless oil. R_f = 0.26 (EtOAc/methanol, 4:1). $[\alpha]_D^{20}$ = +117 (c = 0.9, in CH_2Cl_2). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 6.04 (t, 1H, H-3', $J_{2,3'}$ = $J_{3',4}$ = 1.8 Hz) 5.89 (d, 1H, H-1, $J_{1,2}$ = 4.0 Hz), 5.67 (dt, 1H, H-2, $J_{2,3'}$ = $J_{2,4}$), 5.03–4.98 (m, 1H, H-4), 4.17 (q, 2H, CH_2CH$_3$, J = 7.1 Hz), 3.47–3.42 (m, 2H, CH_2-5), 1.40 (s, 3H, Me, isopr.), 1.33 (s, 3H, Me, isopr.), 1.26 (t, 3H, CH$_2$CH_3) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 165.5 (*C*O), 159.6 (C-3), 116.6 (C-3'), 112.6 (Cq, isopr.), 106.0 (C-1), 81.1 (C-4),

79.5 (C-2), 60.8 (*C*H_2CH$_3$), 56.0 (C-5), 27.7 (Me, isopr.), 27.5 (Me, isopr.), 14.5 (CH$_2$*C*H$_3$) ppm. HRMS: calcd. for $C_{12}H_{19}NO_5$ [*M* + H]$^+$ 258.1336, found 258.1339.

Ethyl (3*Z*)-(5-*N*-Acetylamino-3,5-dideoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ylidene)acetate (4): To a solution of compound **3** (20 mg, 0.08 mmol) in py (0.8 mL), was added Ac_2O (0.4 mL) and the mixture was stirred at room temp. for 5 min. After co-evaporation with toluene, the crude product was purified by CC (EtOAc/petroleum ether, 1:4) to afford the title compound as a colorless oil (21 mg, 90%). R_f = 0.25 (EtOAc/petroleum ether, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.93 (t, 1H, H-3', $J_{2,3'}$ = $J_{3',4}$ = 1.8 Hz), 5.89 (d, 1H, H-1, $J_{1,2}$ = 4.0 Hz), 5.81 (br. t, 1H, NH), 5.77 (br. d, 1H, H-2), 4.91–4.86 (m, 1H, H-4), 4.27–4.18 (m, 2H, C*H*$_2$CH$_3$), 3.84 (ddd, 1H, H-5a, $J_{4,5a}$ = 3.3, $J_{5a,NH}$ = 6.8, $J_{5a,5b}$ = 14.1 Hz), 3.30 (ddd, 1H, H-5b, $J_{4,5b}$ = 5.1, $J_{5b,NH}$ = 7.1 Hz), 1.99 (s, 3H, Me, NHAc), 1.50 (s, 3H, Me, isopr.), 1.41 (s, 3H, Me, isopr.), 1.30 (t, 3H, CH$_2$C*H*$_3$, *J* = 7.1 Hz) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4 (*C*O, Ac), 165.0 (*C*O), 154.1 (C-3), 117.1 (C-3'), 113.0 (Cq, isopr.), 104.6 (C-1), 78.5 (C-4), 78.0 (C-2), 61.0 (*C*H$_2$CH$_3$), 41.1 (C-5), 27.3 (Me, isopr.), 27.1 (Me, isopr.), 23.4 (Me, Ac), 14.2 (CH$_2$*C*H$_3$) ppm. HRMS: calcd. for $C_{14}H_{21}NO_6$ [*M* + Na]$^+$ 322.1261, found 322.1256.

Ethyl (3*Z*)-(1,2-di-*O*-Acetyl-5-*N*-acetylamino-3,5-dideoxy-D-*erythro*-pentofuranos-3-ylidene)acetate (5): A solution of compound **3** (12 mg, 0.05 mmol) in aq. TFA (60%, 0.7 mL) was stirred at room temp. After 10 min, TLC showed complete conversion [R_f = 0.33 (CH_2Cl_2/EtOH, 5:1); R_f (**3**) = 0.5 (CH_2Cl_2/EtOH, 5:1)] and the solution was co-evaporated with toluene. The residue was dissolved in py (0.5 mL) and Ac_2O (0.3 mL) was added. After stirring at room temp. for 5 min, the solvents were co-evaporated with toluene and the crude product was purified by CC (EtOAc) to afford the title compound (13 mg, 80%, ratio α/β: 0.3/1) as a colorless oil. R_f = 0.35 (EtOAc). $[\alpha]_D^{20}$ = +2 (*c* = 0.3, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.50 (d, H-1α, $J_{1,2}$ = 5.1 Hz), 6.21 (s, H-1β), 6.20 (t, H-2β, $J_{2,3'(\beta)}$ = $J_{2,4(\beta)}$ = 1.5 Hz), 6.15 (dt, H-2α), 6.12 (t, H-3'β, $J_{2,3'(\beta)}$ = $J_{3',4(\beta)}$), 6.04 (t, H-3'α, $J_{2,3'(\alpha)}$ = $J_{3',4(\alpha)}$ = 2.5 Hz), 5.91 (br. t, NH-β), 5.82 (br. t, NH-α), 5.00–4.95 (m, H-4β), 4.93–4.87 (m, H-4α), 4.25–4.13 (m, C*H*$_2$CH$_3$, *J* = 7.1 Hz), 3.85 (ddd, H-5aβ, $J_{4,5a\ (\beta)}$ = 3.3, $J_{5a,NH\ (\beta)}$ = 7.3, $J_{5a,5b\ (\beta)}$ = 14.1 Hz), 3.77 (ddd, H-5aα, $J_{4,5a\ (\alpha)}$ = 3.0, $J_{5a,NH\ (\alpha)}$ = 6.3, $J_{5a,5b\ (\alpha)}$ = 14.4 Hz), 3.41 (dt, H-5bα, $J_{4,5b\ (\alpha)}$ = $J_{5b,NH\ (\alpha)}$= 6.3), 3.17

(ddd, H-5bβ), 2.10, 2.09 (2 × s, 6H, Me, Ac, β), 2.08, 2.05 (2 × s, Me, Ac, α), 2.01 (s, 3H, Me, NHAc, β), 1.99 (s, Me, NHAc, α), 1.32 (t, CH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, major anomer, β): δ = 170.4 (*C*O), 169.7 (*C*O), 169.2 (*C*O), 164.1 (*C*O_2Et), 151.5 (C-3), 120.0 (C-3'), 99.6 (C-1), 82.1 (C-4), 74.7 (C-2), 61.3 (CH_2CH_3), 44.6 (C-5), 23.4 (Me, NHAc), 21.4, 20.7 (2 × Me, Ac), 14.3 (CH_2CH_3) ppm. HRMS: calcd. for $C_{15}H_{21}NO_8$ $[M + Na]^+$ 366.1159, found 366.1169.

***N*-[(*S*)-2-(2,5-dihydro-2-oxofuran-4-yl)-2-hydroxyethyl]formamide (6):** A solution of compound **3** (30 mg, 0.12 mmol) in aq. TFA (60%, 1.7 mL) was stirred at room temp. After 10 min, TLC showed complete conversion [R_f = 0.33 (CH_2Cl_2/EtOH, 5:1); R_f (**3**) = 0.5 (CH_2Cl_2/EtOH, 5:1)] and the solution was co-evaporated with toluene. The residue was dissolved in EtOH and water and treated with aq. NaOH solution (0.1 M) until pH 8 was reached [R_f = 0.47 (CH_2Cl_2/EtOH, 5:1]. After evaporation of the solvents, the crude product was purified by CC (CH_2Cl_2/acetone, 3:2) to afford the title compound (9 mg, 45%) as a colorless oil. Alternatively, treatment of the residue with NEt_3 until pH 10 was reached, also led to **6** (39 mg, 65%, starting from 90 mg of **3**). R_f = 0.2 (CH_2Cl_2/acetone, 3:2). $[\alpha]_D^{20}$ = –20 (*c* = 1.3, in MeOH). ^{1}H NMR (400 MHz, [D_6]acetone): δ = 8.16 (s, 1H, CO*H*), 7.50 (br. s, 1H, NH), 6.01 (q, 1H, H-3', $J_{5'a,3'}$ = $J_{5'b,3'}$ = $J_{2,3'}$ = 1.8 Hz), 4.97–4.93 (m, 2H, CH_2-5'), 4.81 (br. t, 1H, H-2, $J_{2,CH2\text{-}1}$ = 5.3 Hz), 3.57 (d, 2H, CH_2-1) ppm. ^{13}C NMR (100 MHz, [D_6]acetone): δ = 173.7 (*C*O, lactone), 172.4 (*C*O), 162.5 (C-4'), 116.0 (C-3'), 71.8 (C-5'), 68.5 (C-2), 43.5 (C-1) ppm. HRMS: calcd. for $C_7H_9NO_4$ $[M + Na]^+$ 194.0424, found 194.0428; calcd. for $C_7H_9NO_4$ $[M + H]$ 170.0459, found 170.0460.

(*S*)-[1-(2,5-dihydro-2-oxofuran-4-yl)-2-*N*-formylamino]ethyl acetate (7): To a solution of compound **6** (21 mg, 0.12 mmol) in py (0.8 mL), was added Ac_2O (0.4 mL) and the mixture was stirred at room temp. for 30 min. After co-evaporation with toluene, the crude product was purified by CC (EtOAc) to afford the title compound as a colorless oil (23 mg, 90%). R_f = 0.17 (EtOAc). $[\alpha]_D^{20}$ = +7 (*c* = 0.7, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (br. s, 1H, CO*H*), 6.13 (br. t, 1H, NH), 6.05 (q, 1H, H-3', $J_{3',5'a}$ = $J_{3',5'b}$ = $J_{2,3'}$ = 1.8 Hz), 5.73 (br. t, 1H, H-2, $J_{2,CH2\text{-}1}$ = 5.0 Hz), 4.89 (br. d, 2H, CH_2-5', *J* = 1.8 Hz), 3.75–3.69 (m, 2H, CH_2-1), 2.16 (s, 3H, CH_3, Ac) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6 (*C*O, lactone), 169.8 (*C*O, Ac), 164.7 (*C*O), 161.5

(C-4'), 117.9 (C-3'), 71.2 (C-5'), 69.1 (C-2), 40.1 (C-1), 20.9 (Me, Ac) ppm. HRMS: calcd. for $C_9H_{11}NO_5$ $[M + H]^+$ 214.0710, found 214.0717; calcd for $[M + Na]^+$ 236.0529, found 236.0537; calcd for $[M + K]^+$ 257.0269, found 257.0278.

(*S*)-[1-(2,5-dihydro-2-oxofuran-4-yl)-2-*N*-formylacetamido]ethyl acetate (8): To a solution of compound **6** (12 mg, 0.07 mmol) in py (1 mL), was added Ac_2O (0.5 mL) and DMAP (3 mg) and the mixture was stirred at room temp. for 1 h. After co-evaporation with toluene, the crude product was purified by CC (EtOAc/petroleum ether, 3:2) to afford the title compound as a colorless oil (15 mg, 84%). R_f = 0.27 (EtOAc/petroleum ether, 3:2). $[\alpha]_D^{20}$ = +8 (c = 0.5, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.11 (br. s, 1H, CO*H*), 6.08 (br. s, 1H, H-3'), 5.87 (br. dd, 1H, H-2, $J_{1a,2}$ = 7.3, $J_{1b,2}$ = 3.5 Hz), 4.92 (br. s, 2H, CH_2-5'), 4.20 (dd, 1H, H-1a, $J_{1a,1b}$ = 13.9 Hz), 3.98 (dd, 1H, H-1b), 2.44 (s, 3H, CH_3, NAc), 2.09 (s, 3H, CH_3, Ac) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4 (*C*O, lactone), 170.9 (*C*O, NAc), 170.0 (*C*O, Ac), 164.3 (*C*O), 162.6 (C-4'), 117.9 (C-3'), 71.0 (C-5'), 68.0 (C-2), 41.7 (C-1), 22.8 (Me, NAc), 20.8 (Me, Ac) ppm. HRMS: calcd. for $C_9H_{11}NO_5$ $[M + H]^+$ 256.0816, found 256.0812; calcd for $[M + Na]^+$ 278.0635, found 278.6276.

Ethyl (3*Z*)-[5-(5-Amine-3,5-anhydro-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-*C*-yl)acetamido-3,5-dideoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ylidene]acetate (9): 50% of compound **3** evolved towards **9** after storage for 1 month at 5 ºC. R_f = 0.29 (EtOAc). $[\alpha]_D^{20}$ = +108 (c = 1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.41 (br. s, 1H, NH), 5.89 (br. s, 1H, H-3'''), 5.87 (d, 1H, H-1', $J_{1',2'}$ = 3.3 Hz), 5.79 (d, 1H, H-1, $J_{1,2}$ = 3.0 Hz), 5.69 (br. d, 1H, H-2'), 4.85 (brd, 1H, H-4'), 4.27–4.16 (m, 3H, H-2, CH_2CH$_3$), 3.84 (brs, 1H, H-4), 3.59 (d, 1H, part A of AB system, 1H, H-5a, $J_{5a,5b}$ = 14.4 Hz), 3.52 (d, part B of AB system, 1H, H-5b), 2.91 (dd, part A of ABX system, 1H, H-5'a, $J_{4',5'a}$ = 2.0, $J_{5'a,5'b}$ = 10.9 Hz), 2.71 (dd, part B of ABX system, 1H, H-5'b, $J_{4',5'b}$ = 8.3 Hz), 2.52 (d, part A of AB system, H-3'a, $J_{3'a,3'b}$ = 16.9 Hz), 2.02 (d, part B of AB system, H-3'b), 1.51, 1.47, 1.39, 1.31 (4 × s, 4 × 3H, Me, isopr.), 1.27 (t, 3 H, CH_2CH_3, J = 7.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.8 (*C*O), 164.9 (*C*O, amide), 155.9 (C-3''), 116.4 (C-3'''), 112.9, 112.7 (2 × Cq, isopr.), 104.8 (C-1'), 104.3 (C-1), 81.8 (C-2), 79.3 (C-4'), 78.3 (C-2'), 74.5 (C-4), 64.5 (C-3), 60.9 (*C*H$_2$CH$_3$), 46.1 (C-5'), 41.5 (C-5), 34.1 (C-3'), 27.4, 27.2, 26.6, 26.5 (4 ×

Me, isopr.), 14.2 (CH_2CH_3) ppm. HRMS: calcd. for $C_{22}H_{32}N_2O_9$ [*M* + H]$^+$ 469,2181, found 469,2185; calcd for [*M* + Na]$^+$ 491.2000, found 491.2008.

Ethyl (3*Z*)-(5-Amino-3,5-dideoxy-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranos-3-ylidene)acetate (10) and 5-Amino-3,5-dideoxy-3-*C*,5-*N*-(1-oxoethan-1-yl-2-ylidene)-1,2-*O*-isopropylidene-α-D-*erythro*-pentopyranose (11): A mixture of compound **2b** (0.523 g, 1.85 mmol) and triphenylphosphine (0.968 g, 3.69 mmol) in H_2O (1.4 mL) and THF (18 mL) was stirred at room temp. for 16 h. After evaporation of the solvents, the residue was chromatographed on silica gel (CH_2Cl_2 then CH_2Cl_2/methanol, 6:1) to afford compound **10** (not isolated due to spontaneous conversion into **11**) and compound **11** (0.372 g, ratio **10**/**11**: 0.35/1, 23% and 67%, respectively). After standing overnight in a CH_2Cl_2 solution, **10** was completely converted into **11** (89% from **2b**).

Data for **10***:* R_f = 0.28 (CH_2Cl_2/methanol, 6:1). ^{1}H NMR (400 MHz, [D$_6$]acetone): δ = 6.02 (t, 1H, H-3', $J_{2,3'} = J_{3',4}$ = 1.8 Hz) 5.84 (d, 1H, H-1, $J_{1,2}$ = 4.8 Hz), 5.67–5.63 (m, 1H, H-4), 5.13 (dt, 1H, H-2), 4.16 (q, 2H, C*H*$_2$CH$_3$, *J* = 7.1 Hz), 3.54 (dd, part A of ABX system, 1H, H-5a, $J_{4,5a}$ = 2.5, $J_{5a,5b}$ = 14.9 Hz), 3.43 (dd, part B of ABX system, 1H, H-5b, $J_{4,5b}$ = 3.3 Hz), 1.34 (s, 3H, Me, isopr.), 1.32 (s, 3H, Me, isopr.), 1.26 (t, 3H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 166.1 (*C*O), 164.1 (C-3), 115.9 (C-3'), 113.1 (Cq, isopr.), 105.3 (C-1), 83.4 (C-2), 82.7 (C-4), 60.9 (*C*H$_2$CH$_3$), 56.0 (C-5), 28.0 (Me, isopr.), 28.0 (Me, isopr.), 14.4 (CH_2CH_3) ppm.

Data for **11***:* R_f = 0.4 (EtOAc). $[\alpha]_D^{20}$ = –8 (*c* = 0.8, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.41 (br. s, 1H, NH), 6.02 (d, 1H, H-1, $J_{1,2}$ = 3.8 Hz), 5.97 (t, 1H, H-3', $J_{2,3'} = J_{3',4}$ = 1.8 Hz) 5.07–5.00 (m, 2H, H-2, H-4), 3.67 (ddd, 1H, H-5a, $J_{4,5a}$ = 5.3, $J_{5a,NH}$ = 7.3, $J_{5a,5b}$ = 11.6 Hz), 3.30 (t, 1H, H-5b, $J_{4,5b}$ = 11.6 Hz), 1.54 (s, 3H, Me, isopr.), 1.38 (s, 3H, Me, isopr.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9 (*C*O, lactam), 152.8 (C-3), 118.9 (C-3'), 114.0 (Cq, isopr.), 107.0 (C-1), 78.7 (C-2), 72.3 (C-2), 45.3 (C-5), 27.2 (Me, isopr.), 26.9 (Me, isopr.) ppm. HRMS: calcd. for $C_{10}H_{13}NO_3$ [*M* + H]$^+$ 212.0917, found 212.0917; calcd for [*M* + Na]$^+$ 234.0737, found 234.0737; calcd for [*M* + K]$^+$ 250.0476, found 250.0477.

5-*N*-Acetylamino-3,5-dideoxy-3-*C*,5-*N*-(1-oxoethan-1-yl-2-ylidene)-1,2-*O*-isopropylidene-α-D-*erythro*-pentopyranose (12): To a solution of compound **11** (15

mg, 0.07 mmol) in py (1 mL), was added Ac_2O (0.6 mL) and DMAP (3 mg) and the mixture was stirred at room temp. for 16 h. After co-evaporation with toluene, the crude product was purified by column chromatography (EtOAc/petroleum ether, 1:3) to afford the title compound as a colorless oil (15 mg, 85%). R_f = 0.32 (EtOAc/petroleum ether, 1:3). $[\alpha]_D^{20}$ = –22 (*c* = 0.8, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.07–6.03 (m, 2H, H-1, H-3', $J_{1,2}$ = 3.8, $J_{2,3'}$ = $J_{3',4}$ = 1.8 Hz), 5.06 (d, 1H, H-2), 5.02 (dd, 1H, H-5a, $J_{4,5a}$ = 6.3, $J_{5a,5b}$ = 11.9 Hz), 4.94 (br. dd, 1H, H-4, $J_{4,5b}$ = 10.9 Hz), 3.06 (t, 1H, H-5b), 2.53 (s, 3H, NAc), 1.55 (s, 3H, Me, isopr.), 1.39 (s, 3H, Me, isopr.) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0 (*C*O), 164.9 (*C*O, lactam), 156.1 (C-3), 119.6 (C-3'), 114.5 (Cq, isopr.), 106.9 (C-1), 78.6 (C-2), 72.2 (C-2), 46.3 (C-5), 27.2 (Me, isopr.), 27.2 (Me, NAc), 26.9 (Me, isopr.) ppm. HRMS: calcd. for $C_{12}H_{15}NO_5$ $[M + H]^+$ 254.1023, found 254.1025; calcd for $[M + Na]^+$ 276.0842, found 276.0844.

Ethyl (3*Z*)-(5-Azido-3,5-dideoxy-D-*erythro*-pentofuranos-3-ylidene)acetate (13): A solution of compound **2a** (0.536 g, 1.89 mmol) in aq. TFA (60%, 13 mL) was stirred at room temp. for 5 min. After co-evaporation with toluene, the crude product was purified by CC (EtOAc/petroleum ether, 1:1) to afford the title compound (0.43 mg, 94%, ratio α/β: 1/0.35) as a colorless oil. R_f = 0.28 (EtOAc/petroleum ether, 2:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.99–5.91 (m, H-3'α, H-3'β, *J* = 2.0 Hz), 5.61 (d, H-1α, $J_{1,2}$ = 5.1 Hz), 5.51 (br. s, 1H, H-1β), 5.06–4.89 (m, H-2α, H-2β, H-4α, H-4β), 4.32-4.18 (m, C*H*$_2$CH$_3$, *J* = 7.1 Hz), 3.66–3.56 (m, H-5aα, H-5aβ, $J_{4,5a\ (\alpha)}$ = 3.3, $J_{5a,5b\ (\alpha)}$= 12.9 Hz), 3.47-3.34 (m, H-5bα, H-5bβ, $J_{4,5b\ (\alpha)}$ = 5.3, $J_{4,5b\ (\beta)}$ = 4.3, $J_{5a,5b\ (\beta)}$ = 13.1 Hz), 1.32 (t, 3, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8 (*C*O), 166.8 (*C*O, β), 161.9 (C-3α), 161.4 (C-3β), 116.7 (C-3'β), 115.9 (C-3'α), 103.5 (C-1β), 96.8 (C-1α), 80.7 (C-4β), 78.6 (C-4α), 73.1 (C-2α), 61.9 (*C*H$_2$CH$_3$, α), 61.6 (*C*H$_2$CH$_3$, β), 55.7 (C-5β), 53.7 (C-5α), 14.2 (CH$_2$*C*H$_3$) ppm. HRMS: calcd. for $C_9H_{13}N_3O_5$ $[M + Na]^+$ 266.0747, found 266.0758.

Ethyl (3*Z*)-[5-Azido-3,5-dideoxy-1-*O*-(*tert*-butyldimethylsilyl)-α-D-*erythro*-pentofuranos-3-ylidene]acetate (14) and Ethyl (3*Z*)-[5-Azido-3,5-dideoxy-1,2-di-*O*-(*tert*-butyldimethylsilyl)-β-D-*erythro*-pentofuranos-3-ylidene]acetate (15): To a solution of compound **13** (37 mg, 0.15 mmol) in dry py (1 mL) was added DMAP (3 mg, 0.02 mmol), and TBDMSCl (0.16 g, 1.06 mmol) at room temp. under argon

atmosphere. After stirring for 15 h at room temp., the reaction was poured into water (3 mL) and the mixture was extracted with EtOAc (3 × 2 mL). Combined organic layers were washed with water and brine and dried with anhydrous $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by CC (EtOAc/petroleum ether, 1:16) to afford **14** (30 mg, 55%) and **15** (10 mg, 14%) and as colorless oils.

Data for **14**: R_f = 0.22 (EtOAc/petroleum ether, 1:16). $[\alpha]_D^{20}$ = +134 (*c* = 1.1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86 (t, 1H, H-3', $J_{2,3'} = J_{3',4}$ = 2.3 Hz), 5.56 (d, 1H, H-1, $J_{1,2}$ = 4.5 Hz), 4.98–4.85 (m, 3H, H-2, H-4, OH), 4.23 (q, 2H, C*H*$_2$CH$_3$, *J* = 7.1 Hz), 3.52 (dd, part A of ABX system, 1H, H-5a, $J_{4,5a}$ = 3.5, $J_{5a,5b}$ = 12.9 Hz), 3.37 (dd, part B of ABX system, 1H, H-5b, $J_{4,5b}$ = 5.3 Hz), 1.31 (t, 3H, CH$_2$C*H*$_3$), 0.92 (s, 9H, *t*Bu, TBDMS), 0.17, 0.16 (2 × s, 6H, Me, TBDMS) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1 (*C*O), 161.5 (C-3), 115.3 (C-3'), 97.3 (C-1), 78.2 (C-4), 74.2 (C-2), 61.4 (*C*H$_2$CH$_3$), 53.7 (C-5), 25.8 (3 × Me, *t*Bu), 18.3 (Cq, *t*Bu), 14.2 (CH$_2$*C*H$_3$), -4.5 (Me, TBDMS), -4.8 (Me, TBDMS) ppm. HRMS: calcd. for $C_{15}H_{27}N_3O_5Si$ [*M* + H]$^+$ 358.1793, found 358.1794; calcd for [*M* + Na]$^+$ 380.1612, found 380.1615.

Data for **15**: R_f = 0.55 (EtOAc/petroleum ether, 1:16). $[\alpha]_D^{20}$ = +13 (*c* = 0.6, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86 (br. d, 1H, H-3'), 5.26–5.22 (m, 2H, H-1, H-2), 4.91–4.85 (m, H-4), 4.29–4.12 (m, 2H, C*H*$_2$CH$_3$), 3.52 (dd, part A of ABX system, 1H, H-5a, $J_{4,5a}$ = 8.3, $J_{5a,5b}$ = 12.6 Hz), 3.21 (dd, part B of ABX system, 1H, H-5b, $J_{4,5b}$ = 4.5 Hz), 1.30 (t, 3H, CH$_2$C*H*$_3$, *J* = 7.1 Hz), 0.87 (s, 9H, *t*Bu, TBDMS), 0.85 (s, 9H, *t*Bu, TBDMS), 0.16, 0.13, 0.12, 0.07 (4 × s, 12H, Me, TBDMS) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8 (*C*O), 159.1 (C-3), 116.0 (C-3'), 103.4 (C-1), 79.5 (C-4), 75.3 (C-2), 60.6 (*C*H$_2$CH$_3$), 56.3 (C-5), 25.8 (3 × Me, *t*Bu), 25.8 (3 × Me, *t*Bu), 18.2 (Cq, *t*Bu), 18.0 (Cq, *t*Bu), 14.4 (CH$_2$*C*H$_3$), -4.2, -4.6, -4.7, 5.1 (4 × Me, TBDMS) ppm. HRMS: calcd. for $C_{21}H_{41}N_3O_5Si_2$ [*M* + Na]$^+$ 494.2477, found 494.2479; calcd for [*M* + K]$^+$ 510.2216, found 510.2209.

Ethyl (3*Z*)-[5-Azido-3,5-dideoxy-1,2-di-*O*-(trimethylsilyl)-β-D-*erythro*-pentofuranos-3-ylidene]acetate (16): To a solution of compound **13** (0.38 g, 1.56 mmol) in dry dichloromethane (15 mL) were added NEt_3 (1.5 mL, 10.9 mmol), DMAP (40 mg), and TMSCl (0.79 mL, 6.24 mmol) at room temp. under argon atmosphere. After stirring for 10 min, TLC showed complete conversion and the reaction mixture was quenched into water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 8

mL) and the combined organic layers were washed with water and dried with $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by CC (EtOAc/cyclohexane, 1:14) to afford the title compound (0.403 g, 67%) as a colorless oil. R_f = 0.31 (EtOAc/cyclohexane, 1:14). $[\alpha]_D^{20}$ = +44 (c = 1.1, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.87 (br. s, 1H, H-3'), 5.22–5.18 (br. d, 2H, H-1, H-2), 4.90–4.84 (m, H-4), 4.26–4.10 (m, 2H, CH_2CH$_3$), 3.49 (dd, part A of ABX system, 1H, H-5a, $J_{4,5a}$ = 8.1, $J_{5a,5b}$ = 12.6 Hz), 3.21 (dd, part B of ABX system, 1H, H-5b, $J_{4,5b}$ = 4.5 Hz), 1.27 (t, 3H, CH$_2$CH_3, J = 7.1 Hz), 0.14 (s, 18H, Me, TMS) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6 (*C*O), 158.7 (C-3), 116.4 (C-3'), 103.4 (C-1), 79.5 (C-4), 75.5 (C-2), 60.5 (*C*H$_2$CH$_3$), 56.0 (C-5), 14.3 (CH$_2$*C*H$_3$), 0.4, 0.1 (Me, TMS) ppm. HRMS: calcd. for $C_{15}H_{29}N_3O_5Si_2$ [M + H]$^+$ 388.1719, found 388.1719; calcd for [M + Na]$^+$ 410.1538, found 410.1538; calcd for [M + K]$^+$ 424.1277, found 424.1279.

Ethyl [5-*N*-(*tert*-Butoxycarbonyl)amino-1,3-dideoxy-D-*erythro*-pentopyran-2-ulos-3-*C*-yl]acetate (17) and Ethyl [*N*-(*tert*-butoxycarbonyl)-1,2-dihydro-pyridin-3-on-4-*C*-yl]acetate (18): To a solution of compound **13** (33 mg, 0.14 mmol) in ethanol (2 mL) was added 10% Pd/C (one spatula point). The mixture was stirred at room temp. under hydrogen atmosphere for 40 min and Boc_2O (50 mg, 0.23 mmol) was added. The resulting mixture was stirred at room temp. for 1 h 30 min, filtered over celite and the solvent was evaporated. After column chromatography (EtOAc/petroleum ether, 2:3 then 3:2), **17** was dissolved in py (2 mL) and Ac_2O (1 mL) was added. The solution was stirred at room temp. for 30 min and then concentrated in vacuum, by co-distillation with toluene. The residue was purified by CC (EtOAc/petroleum ether, 1:4) to afford **18** (16 mg, 42% overall yield) as a colorless oil.

Data for 17: R_f = 0.26 (EtOAc/petroleum ether, 2:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.41–4.35 (m, 1H, H-4), 4.27 (d, 1H, H-1a, $J_{1a,1b}$ = 17.7 Hz), 4.20–4.09 (m, 2H, CH_2CH$_3$), 3.88–3.80 (m, 1H, H-5a), 3.71 (d, 1H, H-1b), 3.01 (ddd, 1H, H-3, $J_{3,4}$ = 2.5, $J_{3,3'a}$ = 5.6 , $J_{3,3'b}$ = 6.8 Hz), 2.90 (dd, 1H, H-3'a, $J_{3'a,3'b}$ = 17.2 Hz), 2.78 (m, 1H, H-5b), 2.53 (dd, 1H, H-3'b), 1.45 (s, 9H, Me, *t*Bu, Boc), 1.25 (t, 3H, CH$_2$CH_3, J = 7.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.6 (*C*O), 173.0 (*C*O), 155.2 (Cq, *t*Bu, Boc), 80.5 (Cq, Boc), 68.3 (C-4), 61.2 (*C*H$_2$CH$_3$), 53.6 (C-1), 30.6 (C-3'), 28.4 (Me, *t*Bu, Boc), 14.2 (CH$_2$*C*H$_3$) ppm. HRMS: calcd. for $C_{14}H_{23}NO_6$ [M + Na]$^+$ 324.1418, found 324.1409; calcd for [M + K]$^+$ 340.1157, found 340.1161.

Data for **18**: R_f = 0.46 (EtOAc/petroleum ether, 2:3). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92 (br. s, 1H, H-5'), 4.28 (br. d, 2H, CH_2-6'), 4.19–4.10 (m, 4H, CH_2-2', CH_2CH$_3$), 3.25 (br. d, 2H, CH_2-2), 1.47 (s, 9H, Me, *t*Bu, Boc), 1.26 (t, 3H, CH$_2$CH_3, J = 7.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.5 (*C*O), 170.7 (*C*O), 81.2 (Cq, *t*Bu, Boc), 61.2 (*C*H$_2$CH$_3$), 51.3 (C-2')*, 42.4 (C-6')*, 34.5 (C-2), 28.5 (Me, *t*Bu, Boc), 14.3 (CH$_2$*C*H$_3$) ppm. HRMS: calcd. for $C_{14}H_{21}NO_5$ $[M + Na]^+$ 306.1312, found 306.1320; calcd for $[M + K]^+$ 322.1051, found 322.1061.

* peaks not observed in the ^{13}C NMR spectrum but clearly identified by HMQC experiments.

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2.4. Carboxymethyl Glycoside Lactones as Synthons for Sugar Derivatives Embodying Conjugated Carbonyl Systems

This subchapter includes the folowing paper:

"Synthesis of Sugars Embodying Conjugated Carbonyl Systems and Related Triazole Derivatives from Carboxymethyl Glycoside Lactones. Evaluation of Their Antimicrobial Activity and Toxicity", Xavier, N. M.; Goulart, M.; Neves, A.; Justino, J.; Chambert, S.; Rauter, A. P.; Queneau, Y. *Bioorg. Med Chem.* **2010**, in press.

and reports on the use of bicyclic lactones derived from carboxymethyl glycosides as synthons towards 3-enopyranosid-2-uloses, 2-*C*-branched-chain conjugated dienepyranosides and related triazole derivatives. The biological activity of the new compounds was evaluated.

The role of the co-autors (besides the supervisors Rauter, A. P. and Queneau, Y.) is specified as follows:

- Goulart, M.; Neves, A. and Justino, J. carried out the biological tests.

- Chambert., S. collaborated in the synthesis of the bicyclic lactone precursors.

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Synthesis of Sugars Embodying Conjugated Carbonyl Systems and Related Triazole Derivatives from Carboxymethyl Glycoside Lactones. Evaluation of Their Antimicrobial Activity and Toxicity

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Keywords: Bicyclic sugar lactones / Sugar enones / Diene pyranosides / 1,2,3-Triazoles / Antimicrobial activity

Abstract

The synthesis of a series of pyranoid derivatives comprising a conjugated carbonyl function and related triazole derivatives, structurally suitable for bioactivity evaluation, was achieved in few steps starting from readily available carboxymethyl glycoside lactones (CMGLs). 3-Enopyranosid-2-uloses were generated by oxidation/elimination of tri-*O*-acylated 2-hydroxy pyranosides. Subsequent Wittig olefination provided stereoselectively 2-*C*-branched-chain conjugated dienepyranosides with (*E*)-configuration around the exocyclic double bond. A heterogeneous CuI/Amberlyst-catalysed "click" chemistry protocol was used to convert glycosides bearing a propargyl moiety into the corresponding 1,2,3-triazoles. These new molecules were screened for their *in vitro* antibacterial and antifungal activities and those containing conjugated

carbonyl systems demonstrated the best efficacy. (***N***-Dodecylcarbamoyl)methyl enone glycerosides were the most active ones among the enones tested. The α-anomer displayed very strong activities against *Bacillus cereus* and *Bacillus subtillis* and strong activity toward *Enterococcus faecalis* and the fungal pathogen *Penicillium aurantiogriseum*. The corresponding β-anomer presented a very strong inhibitory effect against two fungal species (*Aspergillus niger and Penicillium aurantiogriseum*). (*N*-Dodecyl-/*N*-propargyl/ or *N*-Benzylcarbamoyl)methyl dienepyranosides exhibited selectively a strong activity toward *Enterococcus faecalis*. Further acute toxicity evaluation indicated low toxic effect of the (*N*-dodecylcarbamoyl)methyl enone glyceroside α-anomer and of the carbamoylmethyl dienepyranosides *N*-protected with propargyl or benzyl groups.

Introduction

α,β-Unsaturated carbonyl compounds occupy a prominent place among various classes of molecular targets due to their broad spectrum of biological and pharmacological activities [1]. Their conjugated functionality, which is prompted to Michael-type addition, may represent a receptor site for bionucleophiles, notably enzyme sulfhydryl groups [2], and therefore makes them suitable compounds for bioactivity screening. In particular, the incorporation of conjugated carbonyl functions in carbohydrates has led to useful substrates for derivatization in view of their ability to undergo a variety of transformations [3]. Moreover, some of these sugar derivatives have shown significant biological properties. Among them, furanose C-C-linked α,β-unsaturated lactones displayed antifungal [4] and insecticidal effects [5]. These findings have motivated the development of synthetic methodologies towards bicyclic fused derivatives [6] and thiosugar analogues [7]. Sugar enones have also proven to be versatile building blocks for a variety of natural products and relevant chiral molecules, such as branched-chain sugars, *C*-glycosyl compounds or disaccharides [3]. One of the most well-explored enone scaffolds in terms of synthetic uses is levoglucosenone, a 1,6-anhydro-3-enopyran-2-ulose, which is accessible by pyrolysis of cellulose [8]. A few examples of naturally occurring enone-containing sugars have been reported, and those include the fungal metabolites Microthecin [9], a 3-enopyranos-2-ulose which exhibited

antibacterial and cytotoxic effects, and Ascopyrone P [10], a 1-enopyranos-3-ulose known to possess antioxidant and antibacterial activities.

A number of methods for the synthesis of pyranoid enones have appeared in the literature [3] and some of them employ easily available glycals as starting materials. Oxidation of unprotected glycals, e.g. with PDC [11] or $Pd(OAc)_2$ [12], and of their 3-*O*-protected derivatives, using hypervalent iodine reagents [13], leads to 1-enopyranos-3-uloses. Hex-3-enopyranos-2-uloses comprise stereogenic centers next to the conjugated system which may induce stereoselectivity in addition reactions. Enones of this type can be prepared from 2-acyloxyglycal esters by simple transformations, such as chlorination followed by elimination [14], peroxidation and subsequent acetylation [15], or glycosylation of alcohols with these glycal donors in the presence of a Lewis acid [16]. Nevertheless, methods that involve β-acylated hexopyranosuloses as intermediates are preferred since these compounds are prone to undergo β-elimination of acyloxy groups [17]. This tendency for elimination appears to be general and has given rise either to the formation of 1-enopyranos-3-uloses, from easily available furanos-3-uloses [7, 17c], or to 3-enopyranos-2-uloses from the corresponding acylated pyranos-2-uloses [17a-b, 17d]. However methodologies for the synthesis of 2-uloses, which require partially acylated 2-hydroxy pyranosyl precursors, are not straightforward, involving protection and deprotection steps and low global yields. This issue can be overcome starting from carboxymethyl glycoside lactones (CMGLs) [18]. The opening of the lactone moiety of these compounds, especially by amines, has enabled the acquisition of various pseudo glycoconjugates, such as pseudo glycoamino acids [18a], pseudo disaccharides [19], nucleotide sugars [19], pseudo glycolipids [20], or more recently new glycoprobes for membranes nonlinear imaging [21]. Moreover, the connection of the sugar to another molecular block by this strategy provides adducts containing a free and unique hydroxyl group at position 2, available for functionalization [18c].

Thus, we were motivated to explore the feasibility of the oxidation at C-2 of these adducts as concomitant 3,4-elimination would be expected, giving the target 3-enopyranosid-2-uloses. Tri-*O*-acylated 2-hydroxy gluco- and galactopyranosides, which differ in the configuration at C-1, were synthesized and different oxidation methods were used in order to investigate the influence of these factors on the efficiency of the

oxidation-elimination process. Variations on the nature of the aglycon moiety also widened the panel of compounds for subsequent biological acitivity evaluation.

Branching at C-2 of the α-enulosides by Wittig olefination was further accomplished leading to conjugated dienepyranosides. (*N*-Propargylcarbamoyl)methyl glycosides were used for the inclusion of an additional triazole motif, an heterocycle commonly related to a variety of bioactivities, and pyranoid derivatives comprising both the triazole and the conjugated carbonyl system were synthesized. The structural diversity of these highly functionalized pyranosidic derivatives allowed a rational study of their antimicrobial activities. Compounds' acute cytotoxicity in eukaryotic cells was also performed. In this paper both the synthetic work and the results of the biological assays are presented and discussed.

Results and Discussion

1. Chemistry

1.1. Synthesis of 3-Enopyranosid-2-uloses

The α-gluco CMGL **1** was synthesized following the reported procedure based on isomaltulose oxidation followed by acetylation [18a]. The bicyclic lactones having α-galacto (**2**) and β-gluco configuration (**3**) were prepared by anomeric alkylation of glucose or 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose with *tert*-butyl bromoacetate and successive ester cleavage and cyclization [18c]. A series of primary amines were then employed for the lactone ring-opening of CMGLs **1**–**3** (Scheme 1). Propargylamine was chosen aiming to a further derivatization of the terminal triple bond whereas benzylamine and dodecylamine were selected for the connection of a hydrophobic portion to the carbohydrate moiety, in order to investigate their effect in terms of antimicrobial action. The expected amides **4**–**10** were obtained in 66-94% yields, simply by treatment of **1**–**3** with the amines in CH_2Cl_2 at room temperature. Having a free hydroxyl group at C-2, the oxidation/elimination of these adducts was subsequently exploited. The preliminary experiments were carried out with (*N*-propargylcarbamoyl)methyl α-glycosides. For both α-gluco (**4**) and α-galacto (**10**)

derivatives, different oxidizing agents and conditions were used in the search of the most appropriate method (Table 1). The system DMSO/Ac_2O proved to be the most effective one, giving the desired 3-enopyranosid-2-ulose **13** in better yield (ca. 60%) and as the single product. In its ^{13}C NMR spectrum, the carbonyl group was observed at δ = 181.7 ppm, characteristic of an α,β-unsaturated ketone. Diagnostic signals in the ^{1}H NMR spectra were the olefinic proton (H-4), observed at δ = 6.61 ppm as a doublet with a coupling constant $J_{4,5}$ = 1.9 Hz, suggesting the adoption of an ^{O}E envelope (*sofa*) conformation [17b], and H-1, which was assigned at δ 4.99 as a singlet. Moreover, no significant differences in yields were obtained starting from each of the epimers suggesting that configuration at C-4 does not play a crucial role in the reaction outcome. 3,4,6-Tri-*O*-acetyl-glycopyranosid-2-uloses (**11** and **12**) could be detected in the oxidation of **4**/**7** with PDC/Ac_2O, and were the major products when using the Dess-Martin periodinane as milder oxidizing agent. However, isolation of the 2-ulosides was not possible by column chromatography probably due to their facile conversion to the pyranoid enone system.

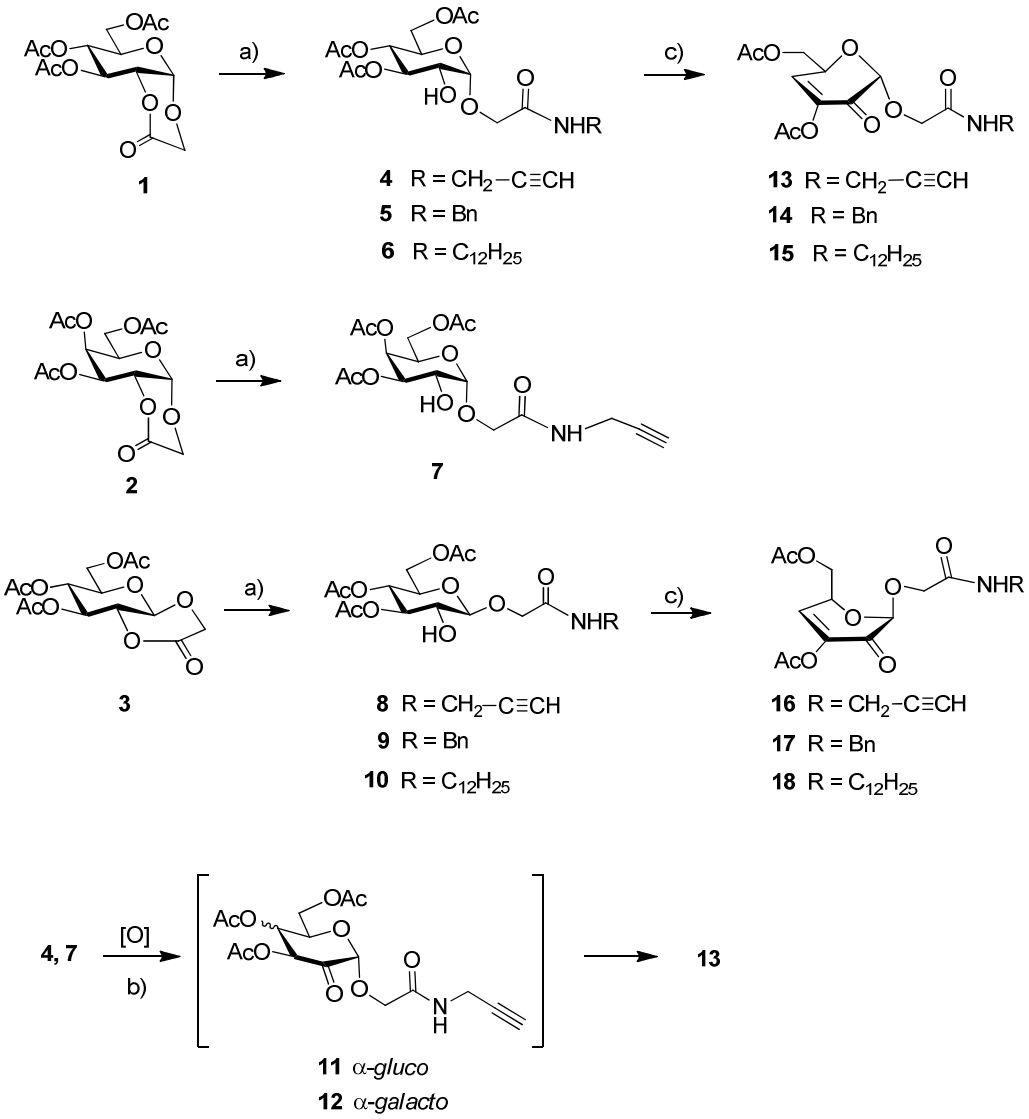
Table 1. Results of the oxidation of (*N*-propargylcarbamoyl)methyl 3,4,6-tri-*O*-acetylglycopyranosides **4** and **10.**

Oxidation Method and Conditions	Yield for **13***	
	4 (*gluco*) ⟶ **13**	**7** (*galacto*) ⟶ **13**
DMSO/Ac_2O, r.t., 16 h	61	59
PDC/Ac_2O, CH_2Cl_2, reflux, 1 h	28 (15)	35 (5)
Dess-Martin Periodinane CH_2Cl_2, r.t., 16 h	6 (15)	6 (22)

*Yield for the obtained 2-uloside (**11**, **12**) indicated in parenthesis.

The DMSO/Ac_2O procedure was thus chosen for the oxidation/elimination of the other glycosides. Hence the α-glucosides bearing benzylcarbamoyl (**5**) and dodecylcarbamoyl moieties (**6**) were converted into the corresponding enones **14**–**15** in nearly quantitative yields.

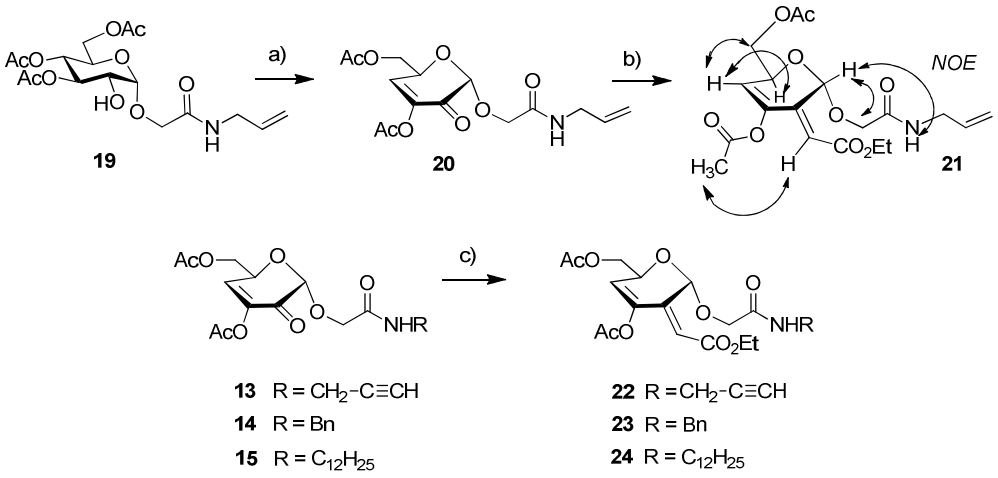
The effect of the anomeric configuration was then examined. Performed under same conditions as those used previously, the DMSO/Ac_2O oxidation of the 2-hydroxy carbamoylmethyl β-glycosides **8**–**10** led to β-3-enopyranosid-2-uloses **16**–**18**, although in lower yields (32–45%) than those obtained for their α-counterparts and with some tendency to undergo decomposition. The results obtained reflect the lower stability of the products formed, due to the adopted E_O envelope conformation, indicated by the values of $J_{4,5}$ (3.3 Hz), involving energetically unfavorable 1,3-diaxial interactions between the substituent at C-1 and the acetoxymethyl group.



Scheme 1. Reactions and conditions: a) RNH_2, CH_2Cl_2, room temp., 16 h, 66–94%; b) see Table 1; c) DMSO/Ac_2O, room temp., 16 h, 96−99% (**14**, **15**), 32–45% (**16**–**18**).

1.2. Synthesis of 2-*C*-Branched-Chain Conjugated Dienepyranosides

Generation of 2-*C*-branched-chain sugars from 3-enopyranosid-2-uloses was subsequently explored. Oxidation of (*N*-allylcarbamoyl)methyl α-glucopyranoside **19** [18c] with DMSO/Ac_2O to enone **20** was followed by Wittig-type treatment with the stabilized ylide [(ethoxycarbonyl)methylene]triphenylphosphorane in chloroform to provide **21** as the single product (Scheme 2). Since no other diastereomer was obtained, which would be helpful for comparison purposes, the (*E)*-configuration around the double bond for **21** was assigned on the basis of its ^{1}H-NMR shift for H-1, which appeared 1.3 ppm downfield from the corresponding signal in **20**, and on NOE experiments, which showed a strong correlation between H-2' and CH_3 (Ac-3) protons. This suggested the given orientation for the ethoxycarbonyl group. Similarly, Wittig olefination of 3-enopyranosid-2-uloses **13**–**15** furnished conjugated dienepyranosides **22**−**24** in moderate yields (54–61%), presenting identical ^{1}H NMR features as those observed for **21**, in accord with the proposed (*E)*-configuration. While a few examples of olefination reactions of pyranoid enones have appeared in the literature [22], to the best of our knowledge there was only one report involving a 3-enopyranoside-2-ulose [22a]. These pyranoid α,β,γ,δ-unsaturated esters are not only interesting for bioactivity studies but may also constitute original templates for further synthetic elaboration through their activated diene system.



Scheme 2. Reactions and conditions: a) DMSO/Ac_2O, room temp., 16 h; b) Ph_3P=$CHCO_2Et$, $CHCl_3$, 40 ºC, 1 h 15 min, 33% overall yield; c) Ph_3P=$CHCO_2Et$, $CHCl_3$, 40 ºC, 1 h–2 h 30 min, 54–61%.

1.3. Synthesis of Triazole Derivatives

Glycosides containing alkynyl moieties were engaged in Cu(I)-catalysed Huisgen 1,3-dipolar cycloadditions with a terminal azide [23] aiming at the insertion of a 1,2,3-triazole ring which is generally recognized as one of the most biologically active motifs amongst heterocyclic nucleus [24]. Various examples of this so-called "click" chemistry employing carbohydrates have been reported, namely in polysaccharide modification [25] or in the synthesis of carbohydrate macrocycles [26], oligosaccharides [27], and glycoconjugates [28], in which the triazole unit may serve as a linker between saccharide moieties, or a spacer entity for the generation of glycopeptide mimics.

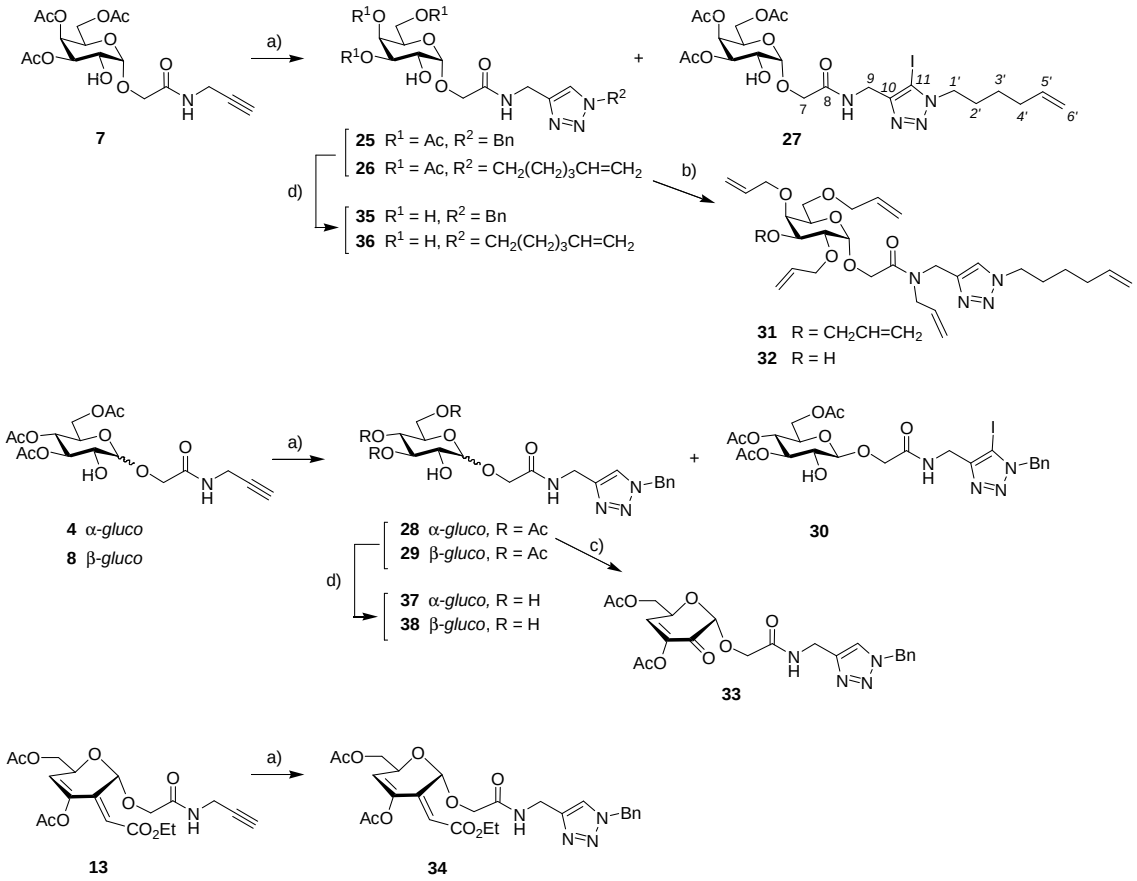
We have applied a mild and simple catalytic procedure consisting on the use of copper(I) iodide supported on Amberlyst A-21 resin and dichloromethane as solvent [29]. The resin is a polystyrene-based polymer containing a dimethylamine group which may serve both as a chelating agent for the cooper salt and as a base [29]. The first attempted cycloaddition reactions between the galactoside **7** and benzyl or hexenyl azide [30] (Scheme 3) were completed after overnight stirring at room temperature and afforded the corresponding 1,2,3-triazole derivatives **25** and **26** in good isolated yields (70-74%). Similar conditions for the coupling of the α- and β-glucosides **4** and **8** with benzyl azide gave successfully the expected triazoles **28** and **29**. Furthermore, "click" reactions that lead to **26** or **29** afforded a small amount (4%) of a secondary product, identified by NMR and HRMS as the 5-iodo-1,2,3-triazole derivatives **27** or **30**, respectively. 5-Iodo triazoles have already been reported as minor products in CuI-catalysed alkyne-azide cycloadditions when organic bases such as NEt_3 or DIPEA (diisopropylethylamine), were used. Their formation may be due to I_2 contamination in CuI, acting as source of I^+ [31]. The role of the base and the influence of its nature in facilitating the formation of 5-iodo triazoles, was recently investigated and a mechanism involving the stabilization of intermediate bis-copper complexes by the base [DMAP (4-dimethylaminopyridine) or DMA (dimethylaniline)], allowing a further intermolecular delivery of iodine, was proposed [32]. Although such a mechanism remains to be clarified, in our case the presence of the basic dimethylamino groups in Amberlyst A-21 seems to be important for the iodination.

This protocol proved to be convenient due to the easy separation of the catalyst from the reaction medium, simply by filtration, and to the fully compatibility with the presence of the acetate functionality, avoiding the addition of base and the use of an organo/aqueous solvent system. To date, only one example of "click" chemistry on carbohydrate templates by means of heterogeneous catalysis was reported, in which Cu(I)-modified zeolites were applied [33].

Variations on the sugar backbone substitution were also carried for investigating its influence on the bioactivity. The replacement of the acetyl protecting groups of **26** by allyl functions was achieved directly, along with OH-2 and *N*-allylation, by treatment with sodium hydride and allyl bromide in DMF at 50 ºC. The fully allylated derivative **31** was thus obtained in 32% overall yield, together with **32,** having a free OH-3 (20%).

The combination of a triazole ring with a conjugated carbonyl system was then undertaken. Thus, oxidation of **28** by the DMSO/Ac_2O method furnished triazole-containing enuloside **33** in reasonable yield (60%). Dienepyranoside **22** was coupled through the alkynyl residue with benzyl azide using CuI/Amberlyst A-21 as catalyst at room temperature to generate the triazole derivative **34** in 87% yield. No competitive cycloaddition at the conjugated system was observed, even though such reactions between azides and α,β-unsaturated esters or conjugated dienes are known to occur, leading to triazolines [34] or aziridines [35].

Deprotection of the triazole-containing glycosides **25**, **26**, **28**, **29** with triethylamine in methanol and water gave **35**–**38** (82 to 95%), a series of compounds bearing a hydrophilic part and a benzyl or a hexenyl moiety as a hydrophobic substituent at position 4 of the triazole ring.



Scheme 3. Reactions and conditions: a) BnN_3 or $N_3CH_2(CH_2)_3CH=CH_2$ (to give **26**), CuI/Amberlyst A-21 (cat.), CH_2Cl_2, room temp., 16 h, 71% (**25**), 74% (**26**, along with **27**, 4%), 60% (**28**), 77% (**29**, along with **30**, 4%), 87% (**34**); b) NaH, CH_2=$CHCH_2Br$, DMF, 50 ºC, 1 h, 32% (**31**) and 20% (**32**); c) DMSO/Ac_2O, room temp., 16 h, 60%; d) NEt_3/H_2O/MeOH, 40 ºC, 16 h, 82-95% (**35**–**38**). Aglycons' carbon atoms numbering do not follow any nomenclature rules and were chosen to simplify the description of the NMR signals.

2. Biological Evaluation

2.1. Antimicrobial activity

The antimicrobial activities of 3-enopyranosid-2-uloses **13**−**15** and **18**, dienepyranosides **21**–**24** and triazole derivatives **25**−**26, 28**−**29, 31**−**38** were investigated using the paper disk diffusion method [36]**.** Their *in vitro* antibacterial activity was evaluated against Gram-negative strains such as *Escherichia coli* and *Salmonella enteritidis*, and the

following Gram-positive bacteria: *Enterococcus faecalis*, *Listeria monocytogenes*, *Staphylococcus aureus*, *Bacillus cereus* and *Bacillus subtilis*. The antifungal activity was studied on a panel of plant pathogenic fungi which may also cause human allergies including *Aspergillus niger*, *Aspergillus brasiliensis*, *Botrytis cinerea and Fusarium solani*, the fungal plant pathogens *Penicillium aurantiogriseum* and *Fusarium culmorum* and the human pathogen *Candida albicans*. The significant results are presented in Table 2. Given the variability of the method, the results are expressed by the average diameter of the inhibition zone detected in two replicates, as well as by the symbols −, +, ++, +++, ++++, +++++, corresponding to a range of diameters, for increasing sensitivity of the microorganism to the substance tested according to Miyazawa et al [37]. Chloramphenicol was used as control for all bacteria tested, whereas for fungi, actidione and amphotericin B were used.

Despite the presence of a triazole nucleous, which is known to play a vital role in the efficacy of many bioactive agents, compounds **25**−**26**, **28**−**29**, **31**−**38** did not show any significant antimicrobial activity in this screening. Pyranoid derivatives bearing conjugated carbonyl systems were found to be the relevant bioactive compounds of this set. From the 3-enopyranosid-2-uloses assayed, only those carrying a dodecyl chain were active (**15**, **18**) and their efficacy proved to be dependent on their anomeric configuration. The α-enuloside 1**5** displayed strong activity against *E. faecalis*, while the β-anomer 1**8** showed virtually no activity at all. Moreover **15** showed a very strong effect against the two species of *Bacillus* tested, with zones of inhibition presenting a diameter similar or greater than that of the standard antibiotic. Moderate and good activities were displayed by **18** against *B. cereus* and *B. subtilis*, respectively. The latter compound was more effective than its α-counterpart toward *S. enteritidis*, showing moderate activity, and toward the fungal pathogen *A. niger*, for which a very strong inhibitory effect was observed. In addition, both enones exhibited similar activity against *Listeria monocytogenes* (moderate effect) and *Penicillium aurantiogriseum*. In the latter case the activities were found to be greater than those of the standard antibiotics.

Dienepyranosides **22**−**24** were shown to selectively inhibit the growth of bacteria, namely a strong activity against *E. faecalis* was detected. Compound **24** was the most active one toward *S. aureus*, with good effect.

Although no complete correlation between bioactivity and structure was found in these series of compounds, one obvious effect is that the bioactivity observed for the 3-enopyran-2-uloses depends strongly on the aglycon moiety. Since enones **13** and **14,** having propargyl and benzyl moieties, did not exhibit any effect, the long and straight chain in **15** and **18** must play a role in eliciting the activity. The hydrophobic portion may allow these molecules to interact with the lipid bilayer of the microorganism cell membrane, or to pass through it. Once inside the lipid membrane or in the cytoplasm, the compound may act by binding to specific targets, especially enzymes involved in key biochemical pathways for microorganism growth. Such inhibition might arise from Michael type addition of enzymes' nucleophilic groups to the enone system, despite the presence of the electron donating acetoxy group at C-3. Concerning dienepyranosides **22**−**24**, the hydrophobic nature of the *N*-substituent does not seem to be a major contributor for the observed bioactivity, with the exception of the effect on *S. aeurus*, a microbe only susceptible to compound **24**.

2.2. Acute Toxicity

In the search for new therapeutic agents, one of the main prerequisites is that the new bioactive molecules should be toxic to the pathogen and exhibit minimal toxicities to the host cells. Hence, our further interest was to evaluate the potential toxicity of the new series of compounds, particularly that of the most bioactive ones. The *in vitro* acute toxicity in eukaryotic cells of all molecules submitted to antimicrobial evaluation was assessed using the MTT cell viability assay [38]. The results quantified as IC_{50} values are summarized in Table 3. Most of the compounds exhibited low toxicity; the higher toxic effect was observed for the β-enuloside **18** with an IC_{50} value of 0.045 mg/mL, while the less toxic molecule appeared to be the triazole-containing dienepyranoside **34** with an IC_{50} value of 12 mg/mL. Among the molecules that displayed significant antimicrobial effects, **18** and **24** (IC_{50} value of 0.076 mg/mL) showed the highest toxicity. The α-enuloside **15** and dienepyranosides **22** and **23** showed low toxic effect, with IC_{50} values of the same order of magnitude as that of the negative control (DMSO).

Table 2. Antimicrobial activitites of the newly synthesized 3-enopyran-2-uloses **15, 18**, and dienepyranosides **22**−**24**.

Compound	**15**		**18**		**22**		**23**		**24**		**Control**[a,b]		**Control**[c]	
	Ø (mm)	inhibition	Ø (mm)	inhibition	Ø (mm)	inhibition	Ø (mm)	inhibition	Ø (mm)	inhibition	Ø (mm)	inhibition	Ø (mm)	inhibition
Bacteria[d]														
Salmonella enteritidis ATCC 13076	<12	–	14	++	<12	–	<12	–	<12	–	41	+++++		
Enterococcus faecalis ATCC 7080	24	++++	<12	–	24	++++	24	++++	22	++++	37	+++++		
Listeria monocytogenes ATCC 19115	17	++	14	++	<12	–	<12	–	<12	–	33	+++++		
Staphylococcus aureus ATCC 6538	17	++	13	+	<12	–	<12	–	20	+++	36	+++++		
Bacillus cereus ATCC 11778	39	+++++	16	++	<12	–	<12	–	<12	–	31	+++++		

Bacillus subtilis ATCC 6633	40	+++++	21	+++	<12	–	<12	–	12	+	40	+++++		
Fungi[d]														
Aspergillus niger ATCC 16404	12	+	40	+++++	<12	–	<12	–	<12	–	43	+++++	22	++++
Penicillium aurantiogriseum ATCC 16025	30	+++++	33	+++++	<12	–	12	+	12	+	26	+++++	26	+++++

Diameter of inhibition zones (∅): +++++, ∅≥26 mm; ++++, 22 mm≤∅<26 mm; +++, 18 mm≤∅<22 mm; ++, 14 mm≤∅<18 mm; +, 12 mm≤∅<14 mm; −, ∅<12mm;

[a]Chloramphenicol for all bacteria tested with the exception of fungi for which [b]actidione and [c]amphotericine B was used;

[d]Microorganisms collection of Microbiology Laboratory from Escola Superior Agrária – Instituto Politécnico de Santarém.

Table 3. IC_{50} values of in vitro acute toxicity of 3-enopyran-2-uloses **13**−**15** and **18**, dienepyranosides **21**−**24** and triazole derivatives **25**−**26, 28**−**29, 32**−**38** in eucaryotic cells using the MTT cell viability assay.

	IC_{50} (mg/mL)	**StDev**
DMSO	0,199	0,037
H_2O_2	0,002	0,002
13	0,282	0,021
14	0,163	0,012
15	0,136	0,010
18	0,045	0,003
21	0.352	0.026
22	0,257	0,019
23	0,128	0,010
24	0,076	0,006
25	0,879	0,066
26	0,063	0,005
28	0,069	0,005
29	0,505	0,038
32	1,186	0,089
33	10,313	0,773
34	11,987	0,899
35	0,617	0,046
36	0,394	0,030
37	0,193	0,014
38	0,426	0,032

Conclusions

Highly functionalized sugar derivatives, structurally suitable for derivatization and for bioactivity screening, namely 3-enopyranosid-2-uloses and 2-*C*-branched-chain dienepyranosides, were straightforwardly accessed starting from CMGLs. Tri-*O*-acylated 2-hydroxy pyranosides, arising from the opening of the bicyclic lactones, were directly converted to the target enones by oxidation/elimination. The anomeric configuration influences the conformational stability of such enulosides and thus the yields obtained for their preparation. A further Wittig-type olefination afforded dienepyranosides with (*E)*-configuration around the exocyclic double bond. Conversion of (*N*-propargylcarbamoyl)methyl glycosides into 1,2,3-triazole derivatives by

cycloaddition with a terminal azide was accomplished in smooth condition using a heterogeneous CuI/Amberlyst catalytic system.

The antimicrobial evaluation demonstrated relevant activity for some of the synthesized enones and diene pyranosides. Only the most hydrophobic enones, i.e. those containing dodecyl chains, were active and different antifungal and antibacterial response was observed for α- and β-anomers. Since the hydrofobicity appears to be essential for the bioactivity of the synthesized enones, is plausible to suppose that their mechanism of action is related to incorporation or penetration across the cell membrane. In both cases binding to specific receptors or enzymes may occur. Although the electrophilicity of the enone system is reduced by the presence of the acetoxy group at C-3, Michael acceptor ability of enones **15**, **18** could be considered to act as a second structural requirement for bioactivity expression, particularly if enzymatic inhibitory activity is involved. Among the dienepyranosides tested, the contribution for the activity of the *N*-substituent hydrophobicity was only observed for *S. aureus*, which was susceptible only to **24**.

The results of acute toxicity indicate that from the nineteen newly synthesized compounds, only four (**18**, **24**, **26**, **28**) can be considered toxic. Compounds **15, 22** and **23**, included among those which exhibited significant antimicrobial activities, showed low toxicity. This encourages further investigation on their use for the control of the pathogens for which efficacy was detected. Moreover, the low acute toxicity observed for most of the molecules screened, motivates the study of their effect towards other therapeutic targets.

Experimental Section

1. Chemistry

General Methods: All reactions were monitored by TLC on Macherei-Nagel 60 F_{254} silica gel aluminium plates with detection under UV light (254 nm) and/or by charring with a solution of 10% H_2SO_4 in EtOH. Column chromatography (CC) was carried out on silica gel 60 (0.040–0.063 mm, Macherey-Nagel). ^{1}H and ^{13}C NMR spectra were acquired with a Bruker ALS 300, DRX300, (300 MHz for ^{1}H and 75 MHz for ^{13}C) or DRX 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer. Chemical shifts are

expressed in parts per million and are referenced to solvent residual peaks. Assignments were made by COSY, HSQC, HMBC and, when necessary, by NOESY experiments. HRMS spectra were recorded by the *Centre Commun de Spectrometrie de Masse*, *Université Claude Bernard Lyon 1* (Villeurbanne) using ESI technique. Optical rotations were measured on a Perkin–Elmer 241 polarimeter at 20 ºC (589 nm, sodium D line). Melting points were determined with a Stuart Scientific SMP 3 apparatus and are uncorrected.

General Procedure for the Opening of the CMGLs with Amines: To a solution of CMGL (0.150 g, 0.43 mmol) in anhydrous CH_2Cl_2 (2.5 mL) was added the amine (0.47 mmol, 1.1 equiv.) and the reaction mixture was stirred overnight at room temp. under nitrogen atmosphere. After concentration under vacuum, the residue was purified by column chromatography (CC) on silica gel.

(*N*-Benzylcarbamoyl)methyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside (5): Reaction of α-CMG lactone **1** [18a] (0.10 g, 0.29 mmol) with *N*-benzylamine according to general procedure gave the title compound (87 mg, 66%) as a colorless oil after purification by CC (from EtOAc/ pentane, 3:2 to EtOAc). R_f = 0.21 (EtOAc/pentane, 1:1). $[\alpha]_D^{20}$ = +60 (c = 0.8, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (t, 1H, NH, J = 5.8 Hz), 7.27−7.12 (m, 5H, Ph), 5.18 (t, 1H, H-3, $J_{2,3} = J_{3,4}$ = 9.8 Hz), 4.90 (t, 1H, H-4, $J_{3,4} = J_{4,5}$ Hz), 4.79 (d, 1H, H-1, $J_{1,2}$ = 3.8 Hz), 4.33−4.23 (m, 3H, CH_2-9, OH), 4.18 (dd, part A of ABX system, H-6a, $J_{5,6a}$ = 4.5, $J_{6a,6b}$ = 12.3 Hz), 4.10−3.87 (m, 4H, H-5, H-6b, CH_2-7, $J_{7a,7b}$ = 15.6 Hz), 3.70−3.61 (m, 1H, H-2), 1.99 (s, 3H, Me, Ac), 1.94 (s, 6H, 2 × Me, Ac) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 170.7, 169.6, 169.3 (3 × *C*O-Ac, *C*O-8), 137.9 (Cq, Ph), 128.6, 127.5, 127.4 (*C*H, Ph), 99.3 (C-1), 73.3 (C-3), 70.2 (C-2), 68.1, 68.0, 67.4 (C-4, C-5, C-7), 61.9 (C-6), 42.8 (C-9), 20.8, 20.7, 20.6 (3 × Me, Ac) ppm. HRMS: calcd. for $C_{21}H_{27}NO_{10}$ $[M + Na]^+$ 476.1533, found 476.1535.

(*N*-Propargylcarbamoyl)methyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (8):
Reaction of β-CMG lactone **3** [18c] (0.11 g, 0.32 mmol) with *N*-propargylamine according to general procedure gave the title compound (0.11, 86%) as a pale oil after purification by CC (from EtOAc/ pentane, 3:2 to 4:1). R_f = 0.35 (EtOAc/pentane, 4:1). $[\alpha]_D^{20}$ = –3 (c = 0.4, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.09−5.01 (m, 2H, H-

3, H-4), 4.41 (d, 1H, H-1, $J_{1,2}$ = 7.9 Hz), 4.37−4.21 (m, 3H, H-6a, CH_2-7, $J_{5,6a}$ = 5.1, $J_{6a,6b}$ = 12.4, $J_{7a,7b}$ = 16.1 Hz), 4.15−4.06 (m, 3H, H-6b, CH_2-9), 3.74−3.62 (m, 2H, H-2, H-5), 2.23 (t, 1H, H-11, J = 2.6 Hz), 2.11 (s, 3H, Me, Ac), 2.09 (s, 3H, Me, Ac), 2.04 (s, 3H, Me, Ac) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 170.8, 169.7, 169.0 (3 × *C*O-Ac, *C*O-8), 103.4 (C-1), 79.2 (C-10), 75.6 (C-3), 72.4, 72.3 (C-2, C-5), 71.8 (C-11), 69.4 (C-7), 67.9 (C-4), 62.0 (C-6), 28.8 (C-9), 21.0, 20.9, 20.8 (3 × Me, Ac) ppm. HRMS: calcd. for $C_{17}H_{23}NO_{10}$ [M + Na]$^+$ 424.1220, found 424.1219.

(*N*-Benzylcarbamoyl)methyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (9): Reaction of β-CMG lactone **3** [18c] (0.15 g, 0.43 mmol) with *N*-benzylamine according to general procedure gave the title compound (0.185 g, 94%) as a colorless oil after purification by CC (EtOAc/ pentane, 3:2 to 4:1). R_f = 0.38 (EtOAc/pentane, 4:1). $[\alpha]_D^{20}$ = –6 (c 0.9, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (t, 1H, NH), 7.29−7.15 (m, 5H, Ph), 5.06−4.93 (m, 2H, H-3, H-4, $J_{2,3}$ = $J_{3,4}$ = $J_{4,5}$ = 9.3 Hz), 4.48 (dd, part A of ABX system, 1H, H-9a, $J_{9a,NH}$ = 6.0, $J_{a,b}$ = 14.9 Hz), 4.40−4.15 (m, 5H, H-1, H-9b, H-6a, CH_2-7, $J_{1,2}$ = 7.8, $J_{5,6a}$ = 4.8, $J_{6a,6b}$ = 12.6, $J_{7a,7b}$ = 15.9, $J_{9b,NH}$ = 5.8 Hz), 4.03 (dd, part B of ABX system, H-6b, $J_{5,6b}$ = 2.0 Hz), 3.64 (ddd, 1H, H-5), 3.57 (dd, 1H, H-2), 2.04 (s, 3H, Me, Ac), 2.03 (s, 3H, Me, Ac), 2.01 (s, 3H, Me, Ac) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 170.7, 169.7, 169.3 (3 × *C*O-Ac, *C*O-8), 137.9 (Cq, Ph), 128.8, 127.7, 127.6 (*C*H, Ph), 103.4 (C-1), 75.2 (C-3), 72.1, 72.0 (C-2, C-5), 69.2 (C-7), 68.1 (C-4), 61.9 (C-6), 43.0 (C-9), 20.9, 20.8, 20.7 (3 × Me, Ac) ppm. HRMS: calcd. for $C_{21}H_{27}NO_{10}$ [M + Na]$^+$ 476.1533, found 476.1533.

(*N*-Dodecylcarbamoyl)methyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (10): Reaction of β-CMG-2-*O*-lactone **3** [18c] (0.107 g, 0.31 mmol) with *N*-dodecylamine according to general procedure gave the title compound (0.146 g, 89%) as a colorless oil after purification by CC (EtOAc/ pentane, 3:2). R_f = 0.31 (EtOAc/pentane, 3:2). $[\alpha]_D^{20}$ = –11 (c = 0.7, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04 (t, 1H, NH, J = 5.7 Hz), 5.08−4.97 (m, 2H, H-3, H-4), 4.38 (d, 1H, H-1, $J_{1,2}$ = 7.9 Hz), 4.31−4.22 (m, 2H, H-6a, H-7a, $J_{5,6a}$ = 5.1, $J_{6a,6b}$ = 12.4, $J_{7a,7b}$ = 15.8 Hz), 4.16 (d, part B of AB system, 1H, H-7b), 4.07 (dd, part B of ABX system, 1H, H-6b, $J_{5,6b}$ = 2.3 Hz), 3.93 (d, 1H, OH), 3.73−3.57 (m, 2H, H-2, H-5), 3.31−3.14 (m, 2H, CH_2-9), 2.07 (s, 3H, Me, Ac), 2.06 (s, 3H, Me, Ac), 2.02 (s, 3H, Me, Ac), 1.54−1.41 (m, 2H, CH_2-10), 1.32−1.19 (m, 18 H, C_9H_{18}),

0.86 (t, 3H, C*H*$_3$-20, *J* = 6.6 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 170.7, 169.7, 169.2 (3 × *C*O-Ac, *C*O-8), 103.3 (C-1), 75.5 (C-3), 72.2, 72.2 (C-2, C-5), 69.1 (C-7), 68.0 (C-4), 62.0 (C-6), 39.3 (C-9), 32.0, 29.7, 29.7, 29.5, 29.4, 29.4, 27.0, 22.8 (C-10–C-19), 20.9, 20.8, 20.7 (2 × Me, Ac), 14.2 (*C*H$_3$-20) ppm. HRMS: calcd. for $C_{26}H_{45}NO_{10}$ $[M + Na]^+$ 554.2941, found 554.2940.

General Procedure for PDC/Ac_2O Oxidation of 4, 7: A solution of 3,4,6-tri-*O*-acetylglycopyranoside (0.1 g, 0.25 mmol) in dry CH_2Cl_2 (0.7 mL) was added to a mixture of PDC (70 mg, 0.19 mmol) and Ac_2O (0.07 mL, 0.8 mmol) in dry CH_2Cl_2 (1.5 mL) under nitrogen atmosphere The resulting mixture was stirred under reflux for 1 h, then cooled to room temp. The solvent was removed in vacuo. The gummy residue was triturated with ethyl acetate (15 mL) and the mixture was filtered through a short pad of Florisil. After evaporation of the solvent, the crude was purified by CC (EtOAc/pentane, 3:2).

General Procedure for Dess-Martin Oxidation of 4, 7: To a solution of 3,4,6-tri-*O*-acetylglycopyranoside (0.3 mmol) in dry CH_2Cl_2 (6 mL) was added Dess-Martin periodinane (0.165 g, 0.39 mmol), and the reaction mixture was stirred overnight at room temp. under nitrogen atmosphere. A saturated $NaHCO_3$ solution was added, and the aqueous phase was extracted twice with dichlorometane. The combined organic layers were washed with water and dried with Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by CC (EtOAc/pentane, 3:2).

(*N*-Propargylcarbamoyl)methyl 3,4,6-tri-*O*-acetyl-α-D-*arabino*-hexopyranosid-2-ulose (11): Oxidation of **4** [18a] with PDC/Ac_2O (0.1 g, 0.25 mmol of **4**) or with Dess-Martin periodinane (0.12 g, 0.3 mmol of **4),** according to general procedures, afforded **11** (15 mg and 18 mg, respectively, 15% yield in both cases), inseparably contaminated with compound **13**. R_f = 0.22 (EtOAc/pentane, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.53 (d, 1H, H-3, $J_{3,4}$ = 9.6 Hz), 5.20 (t, 1H, H-4, $J_{3,4} \sim J_{4,5}$), 5.38, 4.91 (s, 1H, H-1), 4.54−4.49 (d, part A of AB system, H-7a, $J_{7a,7b}$ = 16.9 Hz), 4.38 (d, part B of AB system part, H-7b), 4.34−4.25 (m, 3H, H-5, H-6a, H-9a) 4.16−4.10 (m, 2H, H-6b, H-9b), 2.15 (t, 1H, H-11, *J* = 2.5 Hz), 2.12 (s, 3H, Me, Ac), 2.08 (m, 3H, Me, Ac), 2.08 (s, 3H, Me, Ac) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 170.1, 169.9, 165.7 (2 × *C*O-

Ac, *C*O-8), 97.5 (C-1), 79.5 (C-10), 75.0 (C-3), 70.7 (C-5), 70.4 (C-11), 67.6 (C-4), 66.8 (C-7), 62.2 (C-6), 30.5 (C-9), 21.5, 20.9, 20.8 (3 × Me, Ac) ppm. LRMS (ESI) m/z = 422.1 $[M + Na]^+$, 438.0 $[M + K]^+$, 820.6 $[M_2Na]^+$.

(***N*-Propargylcarbamoyl)methyl 3,4,6-tri-*O*-acetyl-α-D-*lyxo*-hexopyranosid-2-ulose (12):** Oxidation of **7** [18b] with PDC/Ac_2O or with Dess-Martin periodinane according to general procedures, afforded **12** in 5% yield (5 mg, starting from 0.1 g of **7**), and in 22% yield (23 mg, starting from 0.105 g of **7**), respectively, inseparably contaminated with compound **13**. R_f = 0.22 (EtOAc/pentane, 1:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.50 (dd, 1H, H-4, $J_{3,4}$ = 3.5, $J_{4,5}$ = 1.5 Hz), 5.38 (d, 1H, H-3), 4.91 (s, 1H, H-1), 4.56−4.49 (m, 2H, H-5, H-7a, $J_{7a,7b}$ = 16.9 Hz), 4.38 (d, part B of AB system part, H-7b), 4.29 (dd, part A of ABX system, 1H, H-9a, $J_{9a,H\text{-}11}$ = 2.0, $J_{9a,9b}$ = 16.9 Hz), 4.26−4.09 (m, 3H, CH_2-6, H-9b, $J_{5,6a}$ = 6.0, $J_{5,6b}$ = 7.1, $J_{6a,6b}$ = 11.6 Hz), 2.21 (s, 3H, Me, Ac), 2.14−2.10 (m, 4H, H-11, Me, Ac), 2.06 (s, 3H, Me, Ac) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 169.5, 169.1, 165.3 (2 × *C*O-Ac, *C*O-8), 98.7 (C-1), 80.7 (C-10), 71.3 (C-3), 70.2 (C-11), 68.6 (C-5), 67.5 (C-4), 66.8 (C-7), 61.3 (C-6), 30.8 (C-9), 21.3, 20.8, 20.8 (3 × Me, Ac) ppm. HRMS: calcd. for $C_{17}H_{21}NO_{10}$ $[M + Na]^+$ 422.1063, found 422.1059.

General Procedure for DMSO/Ac_2O Oxidation: To a solution of 3,4,6-tri-*O*-acetylglycopyranoside (0.38 mmol) in anhydrous DMSO (25 mL) was added Ac_2O (12.5 mL). The mixture was stirred at room temp. overnight under nitrogen atmosphere. Water (50 mL) was added and the resulting mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with water and brine and dried with Na_2SO_4. After filtration, the solvent was removed under vacuum and the crude was purified by CC.

(***N*-Propargylcarbamoyl)methyl 3,6-di-*O*-acetyl-4-deoxy-α-D-*glycero*-hex-3-enopyranosid-2-ulose (13):** DMSO/Ac_2O oxidation of compound **4** [18a] (0. 123 g, 0.31 mmol) or **7** (0. 15 g, 0.37 mmol) according to general procedure gave the corresponding 3-enopyranosid-2-ulose **13** (63 mg, 61% and 74 mg, 59%, respectively) as a colorless oil after purification by CC (EtOAc/ pentane, 1:1). R_f = 0.31 (EtOAc/pentane, 1:1). $[\alpha]_D^{20}$ = +7 (c = 0.9, in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ =

6.77 (t, 1H, NH), 6.65 (d, 1H, H-4, $J_{4,5}$ = 1.9 Hz), 5.07 (s, 1H, H-1), 4.95 (td, 1H, H-5), 4.42 (dd, part A of ABX system, 1H, H-6a, $J_{5,6a}$ = 5.3, $J_{6a,6b}$ = 11.7 Hz), 4.31 (d, part A of AB system, 1H, H-7a, $J_{7a,7b}$ = 15.3 Hz), 4.22 (dd, part B of ABX system, 1H, H-6b, $J_{5,6b}$ = 4.5 Hz), 4.16 (d, part B of AB system, 1H, H-7b), 4.09−4.02 (m, 2H, C*H*$_2$-9), 2.24 (s, 3H, Me, Ac), 2.23 (t, 1H, H-11, J = 2.6 Hz), 2.08 (s, 3H, Me, Ac) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.7 (*C*O-2), 170.7, 168.0, 167.8 (2 × *C*O-Ac, *C*O-8), 141.9 (C-3), 133.3 (C-4), 98.1 (C-1), 79.1 (C-10), 71.8 (C-11), 68.4, 68.3 (C-5, C-7), 64.3 (C-6), 28.8 (C-9), 20.8, 20.4 (2 × Me, Ac) ppm. HRMS: calcd. for $C_{15}H_{17}NO_8$ [M + Na]$^+$ 362.0852, found 362.0851.

(*N*-Benzylcarbamoyl)methyl 3,6-di-*O*-acetyl-4-deoxy-α-D-*glycero*-hex-3-enopyranosid-2-ulose (14): DMSO/Ac_2O oxidation of compound **5** (80 mg, 0.18 mmol) according to general procedure gave the corresponding 3-enopyranosid-2-ulose **14** (66 mg, 96%) as a colorless oil after purification by CC (EtOAc/ pentane, 3:2). R_f = 0.31 (EtOAc/pentane, 1:1). $[\alpha]_D^{20}$ = +13 (c = 0.7, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.24 (m, 5H, Ph), 6.86 (br. t, 1H, NH), 6.62 (d, 1H, H-4, $J_{4,5}$ = 1.9 Hz), 5.04 (s, 1H, H-1), 4.93 (td, 1H, H-5), 4.51−4.32 (m, 4H, H-6a, H-7a, C*H*$_2$-9, $J_{5,6a}$ = 5.3, $J_{6a,6b}$ = 11.9, $J_{7a,7b}$ = 15.6 Hz), 4.26−4.18 (m, 2H, H-6b, H-7b, $J_{5,6b}$ = 4.5 Hz), 2.24 (s, 3H, Me, Ac), 2.10 (s, 3H, Me, Ac) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.8 (*C*O-2), 170.7, 168.0, 167.9 (2 × *C*O-Ac, *C*O-8), 141.9 (C-3), 137.9 (Cq, Ph), 133.2 (C-4), 128.8, 127.9, 127.7 (*C*H, Ph), 98.2 (C-1), 68.3 (C-5, C-7), 64.4 (C-6), 99.3 (C-1), 73.3 (C-3), 70.2 (C-2), 68.4 (C-5, C-7), 64.3 (C-6), 43.1 (C-9), 20.8, 20.4 (2 × Me, Ac) ppm. HRMS: calcd. for $C_{19}H_{21}NO_8$ [M + Na]$^+$ 414.1165, found 414.1167.

(*N*-Dodecylcarbamoyl)methyl 3,6-di-*O*-acetyl-4-deoxy-α-D-*glycero*-hex-3-enopyranosid-2-ulose (15): DMSO/Ac_2O oxidation of compound **6** [18a] (0. 12 g, 0.23 mmol) according to general procedure gave the corresponding 3-enopyranosid-2-ulose **15** (0.105 g, 99%) as a yellow oil after purification by CC (EtOAc/ pentane, 1:1). R_f = 0.25 (EtOAc/pentane, 2:3); $[\alpha]_D^{20}$ = +30 (c = 1, in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.65 (d, 1H, H-4, $J_{4,5}$ = 1.9 Hz), 6.49 (t, 1H, NH), 5.02 (s, 1H, H-1), 4.95 (td, 1H, H-5), 4.42 (dd, part A of ABX system, 1H, H-6a, $J_{5,6a}$ = 5.5, $J_{6a,6b}$ = 11.8 Hz), 4.31−4.21 (m, 2H, H-6b, H-7a, $J_{5,6b}$ = 4.5, $J_{7a,7b}$ = 15.1 Hz), 4.15 (d, part B of AB system, 1H, H-7b), 3.33−3.18 (m, 2H, C*H*$_2$-9), 2.26 (s, 3H, Me, Ac), 2.10 (s, 3H, Me, Ac), 1.55−1.45

(m, 2H, C*H*$_2$-10), 1.33−1.20 (m, 18 H, C$_9$*H*$_{18}$), 0.86 (t, 3H, C*H*$_3$-20, J = 7.1 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.9 (*C*O-2), 170.7, 167.9, 167.8 (2 × *C*O-Ac, *C*O-8), 142.0 (C-3), 133.2 (C-4), 98.2 (C-1), 68.3 (C-5, C-7), 64.4 (C-6), 39.3 (C-9), 32.0, 29.8, 29.7, 29.6, 29.5 29.4, 29.4, 27.0, 22.8 (C-10–C19), 20.8 , 20.4 (2 × Me, Ac), 14.2 (*C*H$_3$-20) ppm. HRMS: calcd. for $C_{24}H_{39}NO_8$ [M + Na]$^+$ 492.2573, found 492.2574.

(*N*-Propargylcarbamoyl)methyl 3,6-di-*O*-acetyl-4-deoxy-β-D-*glycero*-hex-3-enopyranosid-2-ulose (16): DMSO/Ac_2O oxidation of compound **8** (0.1 g, 0.25 mmol) according to general procedure gave the corresponding 3-enopyranosid-2-ulose **16** (27 mg, 32%) as a colorless oil after purification by CC (EtOAc/ pentane, 3:2). R_f = 0.48 (EtOAc/pentane, 4:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.00 (t, 1H, NH), 6.70 (d, 1H, H-4, $J_{4,5}$ = 3.0 Hz), 5.07 (s, 1H, H-1), 4.95−4.89 (ddd, 1H, H-5), 4.47−4.25 (m, 3H, H-6a, H-6b, H-7a, $J_{5,6a}$ = 6.6, $J_{5,6b}$ = 4.9, $J_{6a,6b}$ = 11.7, $J_{7a,7b}$ = 15.7 Hz), 4.21 (d, part B of AB system, 1H, H-7b), 4.12−4.06 (m, 2H, C*H*$_2$-9), 2.27 (s, 3H, Me, Ac), 2.23 (t, 1H, H-11, J = 2.6 Hz), 2.12 (s, 3H, Me, Ac) ppm. HRMS: calcd. for $C_{15}H_{17}NO_8$ [M + Na]$^+$ 362.0852, found 362.0852.

(*N*-Benzylcarbamoyl)methyl 3,6-di-*O*-acetyl-4-deoxy-β-D-*glycero*-hex-3-enopyranosid-2-ulose (17): DMSO/Ac_2O oxidation of compound **9** (0.11 g, 0.24 mmol) according to general procedure gave the corresponding 3-enopyranosid-2-ulose **17** (42 mg, 45%) as a colorless oil after purification by CC (from EtOAc/ pentane, 3:2 to 4:1). R_f = 0.49 (EtOAc/pentane, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36−7.24 (m, 5H, Ph), 7.13 (br. t, 1H, NH), 6.67 (d, 1H, H-4, $J_{4,5}$ = 3.0 Hz), 5.05 (s, 1H, H-1), 4.89 (ddd, 1H, H-5), 4.53−4.33 (m, 4H, H-6a, H-7a, C*H*$_2$-9, $J_{7a,7b}$ = 15.4, $J_{9,NH}$ = 5.8, $J_{9a,9b}$ = 9.2 Hz), 4.32−4.18 (m, 2H, H-6b, H-7b, $J_{5,6b}$ = 5.1, $J_{6a,6b}$ = 11.7 Hz), 2.24 (s, 3H, Me, Ac), 2.08 (s, 3H, Me, Ac). HRMS: calcd. for $C_{19}H_{21}NO_8$ [M + Na]$^+$ 414.1165, found 414.1165.

(*N*-Dodecylcarbamoyl)methyl 3,6-di-*O*-acetyl-4-deoxy-β-D-*glycero*-hex-3-enopyranosid-2-ulose (18): DMSO/Ac_2O oxidation of compound **10** (0.1 g, 0.19 mmol) according to general procedure gave the corresponding 3-enopyranosid-2-ulose **18** (33 mg, 37%) as a colorless oil after purification by CC (from EtOAc/pentane, 3:2 to 4:1). R_f = 0.43 (EtOAc/pentane, 3:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.74 (t, 1H, NH),

6.69 (d, 1H, H-4, $J_{4,5}$ = 3.2 Hz), 5.03 (s, 1H, H-1), 4.94−4.87 (m, 1H, H-5), 4.43−4.26 (m, 3H, H-6a, H-6b, H-7a, $J_{5,6a}$ = 6.8, $J_{5,6b}$ = 5.1, $J_{6a,6b}$ = 11.5, $J_{7a,7b}$ = 15.5 Hz), 3.31−3.22 (m, 2H, CH_2-9), 2.26 (s, 3H, Me, Ac), 2.11 (s, 3H, Me, Ac), 1.57−1.44 (m, 2H, CH_2-10), 1.33−1.21 (m, 18 H, C_9H_{18}), 0.87 (t, 3H, CH_3-20, J = 6.8 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 182.5 (*C*O-2), 170.6, 168.3, 168.0 (2 × *C*O-Ac, *C*O-8), 142.4 (C-3), 133.1 (C-4), 99.1 (C-1), 71.2, 68.7 (C-5, C-7), 65.2 (C-6), 39.3 (C-9), 32.0, 29.8, 29.7, 29.6, 29.5, 29.4, 27.0, 22.8 (C-10–C19), 20.8, 20.4 (2 × Me, Ac), 14.2 (*C*H_3-20) ppm. HRMS: calcd. for $C_{24}H_{39}NO_8$ $[M + Na]^+$ 492.2573, found 492.2574.

General Procedure for Wittig Olefination of 3-Enopyranosid-2-uloses: To a solution of 3-enopyranosid-2-ulose (0.10 mmol) in $CHCl_3$ (1 mL) was added [(ethoxycarbonyl)methylene]triphenylphosphorane (45 mg, 0.13 mmol). The whole solution was stirred at 40 ºC until complete conversion, as indicated by TLC. The solvent was removed under vacuum and the residue was purified by column chromatography on silica gel.

(*N*-Allylcarbamoyl)methyl 3,6-di-*O*-acetyl-4-deoxy-β-D-*glycero*-hex-3-enopyranosid-2-ulose (20) and (*N*-Allylcarbamoyl)methyl 3,6-di-*O*-acetyl-2,4-dideoxy-2-*C*-[(*E*)-(ethoxycarbonyl)methylene]-α-D-*glycero*-hex-3-enopyranoside (21): DMSO/Ac_2O oxidation of compound **19** [18c] (75 mg, 0.19 mmol) to 3-enopyranosid-2-ulose **20** was performed according to general procedure. After CC (EtOAc/pentane, 3:2), **20** was subjected to Wittig olefination which was completed within 1 h 15 min. Purification by CC (from Et_2O/hexane, 9:1 to Et_2O) afforded **21** (25 mg, 33% overall yield), as white solid.

Data for **20**: R_f = 0.42 (EtOAc/pentane, 3:2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.65 (d, 1H, H-4, $J_{4,5}$ = 1.9), 6.61 (br. t, 1H, NH), 5.91−5.74 (m, 1H, H-10), 5.24−5.01 (m, 2H, CH_2-11), 5.04 (s, 1H, H-1), 4.96 (td, 1H, H-5), 4.42 (dd, part A of ABX system, 1H, H-6a, $J_{5,6a}$ = 5.3, $J_{6a,6b}$ = 11.7 Hz), 4.32 (d, part A of AB system, 1H, H-7a, $J_{7a,7b}$ = 15.3 Hz), 4.23 (dd, part B of ABX system, 1H, H-6b, $J_{5,6a}$ = 4.7 Hz), 4.18 (d, part B of AB system 1H, H-7b) 3.95−3.87 (m, 2H, CH_2-9), 2.25 (s, 3H, Me, Ac), 2.10 (s, 3H, Me, Ac) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.8 (*C*O-2), 170.7, 167.9, 167.9 (2×*C*O-Ac, *C*O-8), 141.9 (C-3), 133.3, 133.5 (C-4, C-10), 116.8 (C-11) 98.2 (C-1), 68.3, 68.3 (C-5, C-7), 64.3 (C-6), 41.5 (C-9), 20.8, 20.4 (2 × Me, Ac) ppm.

Data for **21:** R_f = 0.24 (EtOAc/pentane, 2:3). m.p. 101–103 ºC. $[\alpha]_D^{20}$ = +50 (c 0.7, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.11 (t, 1H, NH), 6.39 (s, 1H, H-1), 5.95 (dd, 1H, H-4, $J_{2',4}$ = 0.8, $J_{4,5}$ = 2.0 Hz), 5.91 (br. d, 1H, H-2'), 5.89−5.80 (m, 1H, H-10), 5.19 (dq, 1H, H-11a, $J_{11a,11b}$ = $J_{9a,11a}$ = $J_{9b,11a}$= 1.5, $J_{10,11a}$ = 17.1 Hz), 5.11 (dq, 1H, H-11b, $J_{9a,11b}$ = $J_{9b,11b}$ = $J_{11a,11b}$, $J_{10,11b}$ = 10.3 Hz), 4.72 (ddd, 1H, H-5), 4.40−4.30 (m, 2H, H-6a, H-7a, $J_{5,6a}$ = 5.8, $J_{6a,6b}$ = 11.8, $J_{7a,7b}$ = 15.6 Hz), 4.27 (d, part B of AB system, 1H, H-7b), 4.23-4.15 (m, 2H, H-6b, C*H*$_2$CH$_3$, $J_{5,6a}$ = 4.3, J = 7.1 Hz), 3.97-3.91 (m, 2H, C*H*$_2$-9), 2.27 (s, 3H, Me, Ac), 2.10 (s, 3H, Me, Ac), 1.29 (t, 3H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.9, 168.9, 168.0 (2 × *C*O-Ac, *C*O-8), 165.4 (*C*O), 142.1, 140.3 (C-2, C-3), 134.2 (C-10), 121.4 (C-4), 116.4 (C-11), 114.3 (C-2'), 94.2 (C-1), 67.1, 66.7 (C-5, C-7), 64.9 (C-6), 61.2 (*C*H$_2$CH$_3$), 41.5 (C-9), 21.0, 20.9 (2 × Me, Ac), 14.3 (CH$_2$*C*H$_3$) ppm. HRMS: calcd. for $C_{19}H_{25}NO_9$ [*M* + Na]$^+$ 434.1427, found 434.1426.

(*N*-Propargylcarbamoyl)methyl 3,6-di-*O*-acetyl-2,4-dideoxy-2-*C*-[(*E*)-(ethoxycarbonyl)methylene]-α-D-*glycero*-hex-3-enopyranoside (22): Wittig olefination of the 3-enopyranosid-2-ulose **13** (28 mg, 0.08 mmol) according to general procedure, was completed within 2 h 30 min. The title compound was obtained as a white solid (19 mg, 56%) after purification by CC (diethyl ether/hexane, 9:1 to diethyl ether). R_f = 0.30 (EtOAc/pentane, 2:3), m.p. 106–108 ºC, $[\alpha]_D^{20}$ = +31 (c = 0.4, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (t, 1H, NH), 6.38 (s, 1H, H-1), 5.95 (dd, 1H, H-4, $J_{2',4}$ = 1.0, $J_{4,5}$ = 2.0 Hz), 5.92 (br. d, 1H, H-2'), 4.72 (ddd, 1H, H-5), 4.39−4.31 (m, 2H, H-6a, H-7a, $J_{5,6a}$ = 5.8, $J_{6a,6b}$ = 11.8, $J_{7a,7b}$ = 15.6 Hz), 4.29−4.14 (m, 4H, H-6b, H-7b, C*H*$_2$CH$_3$, $J_{5,6a}$ = 4.3, J = 7.1 Hz), 4.13−4.06 (m, 2H, C*H*$_2$-9, $J_{H\text{-}9,H\text{-}11}$ = 2.5, $J_{H\text{-}9,NH}$ = 5.5 Hz), 2.27 (s, 3H, Me, Ac), 2.19 (t, 1H, H-11), 2.10 (s, 3H, Me, Ac), 1.31 (t, 1H, CH$_2$C*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 168.9, 168.0 (2 × *C*O-Ac, *C*O-8), 165.5 (*C*O), 142.1, 140.2 (C-2, C-3), 121.4 (C-4), 114.4 (C-2'), 94.3 (C-1), 79.6 (C-10), 71.3 (C-11), 67.1, 66.7 (C-5, C-7), 64.9 (C-6), 61.3 (*C*H$_2$CH$_3$), 28.6 (C-9), 20.9, 20.9 (2 × Me, Ac), 14.3 (CH$_2$*C*H$_3$) ppm. HRMS: calcd. for $C_{19}H_{23}NO_9$ [*M* + Na]$^+$ 432.1271, found 432.1272.

(*N*-Benzylcarbamoyl)methyl 3,6-di-*O*-acetyl-2,4-dideoxy-2-*C*-[(*E*)-(ethoxycarbonyl) methylene]-α-D-*glycero*-hex-3-enopyranoside (23): Wittig olefination of the 3-enopyranosid-2-ulose **14** (40 mg, 0.1 mmol) according to general procedure, was

completed within 2 h. The title compound was obtained as a white solid (29 mg, 61%) after purification by CC (diethyl ether/hexane, 7:3 to diethyl ether). R_f = 0.23 (EtOAc/pentane, 2:3). m.p. 123–125 ºC. $[\alpha]_D^{20}$ = +27 (c = 0.3, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (t, 1H, NH), 7.32−7.28 (m, 3H, Ph), 7.27−7.25 (m, 2H, Ph), 6.38 (s, 1H, H-1), 5.93 (dd, 1H, H-4, $J_{2',4}$ = 1.0, $J_{4,5}$ = 2.3 Hz), 5.86 (br. d, 1H, H-2'), 4.70 (ddd, 1H, H-5), 4.54 (dd, part A of ABX system, H-9a, $J_{9a,NH}$ = 6.0, $J_{9a,9b}$ = 14.9 Hz), 4.46 (dd, part B of ABX system, H-9b, $J_{9b,NH}$ = 5.8 Hz), 4.41−4.32 (m, 2H, H-6a, H-7a, $J_{5,6a}$ = 5.8, $J_{6a,6b}$ = 11.6, $J_{7a,7b}$ = 15.6 Hz), 4.29 (d, part B of AB system, H-7a), 4.16 (dd, part B of ABX system, H-6b, $J_{5,6b}$ = 4.0 Hz), 4.10−3.97 (m, 2H, C*H*$_2$CH$_3$), 2.24 (s, 3H, Me, Ac), 2.10 (s, 3H, Me, Ac), 1.21 (t, 1H, CH$_2$C*H*$_3$, J = 7.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 169.0, 168.0 (2 × *C*O-Ac, *C*O-8), 165.4 (*C*O), 142.1, 140.3 (C-2, C-3), 138.3 (Cq, Ph), 128.6, 128.0, 127.4 (*C*H, Ph), 121.4 (C-4), 114.3 (C-2'), 94.3 (C-1), 67.1, 66.6 (C-5, C-7), 64.9 (C-6), 61.2 (*C*H$_2$CH$_3$), 43.1 (C-9), 20.9, 20.9 (2 × Me, Ac), 14.2 (CH$_2$*C*H$_3$) ppm. HRMS: calcd. for $C_{23}H_{27}NO_9$ [M + Na]$^+$ 484.1584, found 484.1591.

(*N*-Dodecylcarbamoyl)methyl 3,6-di-*O*-acetyl-2,4-dideoxy-2-*C*-[(*E*)-(ethoxycarbonyl)methylene]-*α*-D-*glycero*-hex-3-enopyranoside (24): Wittig olefination of the 3-enopyranosid-2-ulose **15** (40 mg, 0.09 mmol) according to general procedure, was completed within 1 h. The title compound was obtained as a white solid (25 mg, 54%) after purification by CC (diethyl ether/hexane, 4:1 to diethyl ether). R_f = 0.43 (EtOAc/pentane, 2:3). $[\alpha]_D^{20}$ = +26 (c = 0.5, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.04 (t, 1H, NH), 6.37 (s, 1H, H-1), 5.95 (dd, 1H, H-4, $J_{2',4}$ = 0.8, $J_{4,5}$ = 2.0 Hz), 5.91 (br. d, 1H, H-2'), 4.71 (ddd, 1H, H-5), 4.37 (dd, part A of ABX system, H-6a, $J_{5,6a}$ = 5.8, $J_{6a,6b}$ = 11.6 Hz), 4.31 (d, part A of AB system, H-7a, $J_{7a,7b}$ = 15.6 Hz), 4.26−4.14 (m, 4H, H-6b, H-7b, C*H*$_2$CH$_3$, $J_{5,6a}$ = 4.3, J = 7.1 Hz), 3.32−3.24 (m, 2H, C*H*$_2$-9), 2.27 (s, 3H, Me, Ac), 2.10 (s, 3H, Me, Ac), 1.57−1.47 (m, 2H, C*H*$_2$-10), 1.34−1.20 (m, 21 H, CH$_2$C*H*$_3$, C$_9$*H*$_{18}$), 0.88 (t, 3H, C*H*$_3$-20, J = 7.1 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 168.9, 168.0 (2 × *C*O-Ac, *C*O-8), 165.4 (*C*O), 142.1, 140.4 (C-2, C-3), 121.4 (C-4), 114.3 (C-2'), 94.1 (C-1), 67.1, 66.6 (C-5, C-7), 64.9 (C-6), 61.2 (*C*H$_2$CH$_3$), 39.3 (C-9), 32.1, 29.8, 29.8, 29.5, 29.5, 27.1, 22.8 (C-10–C-19), 20.9 , 20.9 (2 × Me, Ac), 14.3 (CH$_2$C*H*$_3$), 14.3 (*C*H$_3$-20) ppm. HRMS: calcd. for $C_{28}H_{45}NO_9$ [M + Na]$^+$ 562.2992, found 562.2996.

General Procedure for the CuI/Amberlyst A21-Catalyzed Cycloaddition of (*N*-Propargylcarbamoyl)methyl Glycosides with a Terminal Azide: To a solution of (*N*-propargylcarbamoyl)methyl glycoside (0.17 mmol) in dichloromethane (1.5 mL) was added azide (0.2 mmol) and CuI/Amberlyst A21 catalyst 0.8 mmol/g (17 mg, 0.08 equiv.). The suspension was stirred at room. temp. overnight. After filtration of the catalyst and evaporation of the solvent, the crude was purified by CC.

{[*N*-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]carbamoyl}methyl 3,4,6-tri-*O*-acetyl-α-D-galactopyranoside (25): CuI/Amberlyst A21-catalysed coupling of (*N*-propargylcarbamoyl)methyl glycoside **7** (0.07 g, 0.17 mmol) with benzyl azide according to general procedure gave the triazole derivative **25** (66 mg, 71%) as a colorless oil after purification by CC (from EtOAc to EtOAc/methanol, 9:1). R_f = 0.22 (EtOAc). $[\alpha]_D^{20}$ = +92 (c = 1.3, in CH_2Cl_2). H NMR (400 MHz, $CDCl_3$): δ = 8.29 (br. s, 1H, NH), 7.50 (br. s, 1H, H-11), 7.38−7.31 (m, 3H, Ph), 7.26−7.21 (m, 2H, Ph), 5.44 (s, 2H, C*H*$_2$Ph), 5.39 (br. d, 1H, H-4), 5.21 (dd, 1H, H-3, $J_{2,3}$ = 10.6, $J_{3,4}$ = 3.3 Hz), 4.92 (d, 1H, H-1, $J_{1,2}$ = 3.8 Hz), 4.55 (brd, part A of ABX system, H-9a, $J_{9a,9b}$ = 12.8 Hz), 4.32 (brd, part B of ABX system, H-9b), 4.25−4.18 (m, 2H, H-5, H-7a), 4.10−4.00 (m, 4H, H-2, H-6a, H-6b, H-7b), 2.10 (s, 3H, Me, Ac), 2.01 (s, 3H, Me, Ac), 1.97 (s, 3H, Me, Ac) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 170.6, 170.2, 169.5 (3 × *C*O-Ac, *C*O-8), 134.2 (Cq, Ph), 129.3, 129.0, 128.3 (*C*H, Ph), 100.0 (C-1), 70.1 (C-3), 68.1, 67.6, 67.3 (C-4, C-5, C-7), 66.5 (C-2), 61.8 (C-6), 54.5 (C-1'), 34.1 (C-9), 20.9, 20.8, 20.7 (3 × Me, Ac) ppm. HRMS: calcd. for $C_{24}H_{30}N_4O_{10}$ [*M* + Na]$^+$ 557.1860, found 557.1861.

({*N*-[1-(Hex-5-en-1-yl)-1*H*-1,2,3-triazol-4-yl]methyl}carbamoyl)methyl 3,4,6-tri-*O*-acetyl-α-D-galactopyranoside (26) and ({*N*-[1-(hex-5-en-1-yl)-5-iodo-1,2,3-triazol-4-yl]methyl}carbamoyl)methyl 3,4,6-tri-*O*-acetyl-α-D-galactopyranoside (27): CuI/Amberlyst A21-catalysed coupling of (*N*-propargylcarbamoyl)methyl glycoside **7** (0.099 g, 0.25 mmol) with 5-hexenyl azide according to general procedure gave the triazole **26** (96 mg, 74%) and its 5-iodo triazole derivative **27** (7 mg, 4%) as colorless oils after purification by CC (from EtOAc to EtOAc/methanol, 9:1).

Data for **26**: R_f = 0.22 (EtOAc). $[\alpha]_D^{20}$ = +71 (c = 0.8, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (t, 1H, NH), 7.55 (s, 1H, H-11), 5.78−5.66 (m, 1H, H-5'), 5.38 (br. d,

1H, H-4, $J_{3,4}$ = 3.3, $J_{4,5}$ = 1.0 Hz), 5.21 (dd, 1H, H-3, $J_{2,3}$ = 10.6 Hz), 5.05 (br. d, 1H, OH), 5.01−4.92 (m, 2H, H-6'a, H-6'b), 4.91 (d, 1H, H-1, $J_{1,2}$ = 3.5 Hz), 4.58 (dd, part A of ABX system, 1H, H-9a, $J_{9a,NH}$ = 6.3, $J_{9a,9b}$ = 15.4 Hz), 4.38−4.18 (m, 5H, H-5, H-7a, H-9b, H-1'a, H-1'b, $J_{7a,7b}$ = 15.6 Hz), 4.10−4.00 (m, 4H, H-2, H-6a, H-6b, H-7b), 2.12−2.03 (m, 5H, CH_2-4', Me, Ac), 2.01 (s, 3H, Me, Ac), 1.97 (s, 3H, Me, Ac), 1.91-1.82 (m, 2H, CH_2-2'), 1.44-1.34 (m, 2H, CH_2-3') ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 170.5, 170.2, 169.5 (3 × *C*O-Ac, *C*O-8), 144.6 (C-10), 137.7 (C-5'), 122.4 (C-11), 115.5 (C-6'), 100.0 (C-1), 70.1 (C-3), 68.1 (C-4), 67.6, (C-7), 67.2 (C-5), 66.5 (C-2), 61.8 (C-6), 50.4 (C-1'), 34.0 (C-9), 33.0 (C-4'), 29.5 (C-2'), 25.7 (C-3'), 20.9, 20.8, 20.7 (3 × Me, Ac) ppm. HRMS: calcd. for $C_{23}H_{34}N_4O_{10}$ [*M* + Na]$^+$ 549.2173, found 549.2174.

Data for **27**: R_f = 0.48 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (t, 1H, NH), 5.91−5.66 (m, 1H, H-5'), 5.43 (dd, 1H, H-4, $J_{3,4}$ = 3.3, $J_{4,5}$ = 1.0 Hz), 5.26 (dd, 1H, H-3, $J_{2,3}$ = 10.5 Hz), 5.09−4.96 (m, 2H, H-6'a, H-6'b), 4.93 (d, 1H, H-1, $J_{1,2}$ = 3.7 Hz), 4.79 (dd, part A of ABX system, 1H, H-9a, $J_{9a,NH}$ = 7.6, $J_{9a,9b}$ = 15.9 Hz), 4.44 (br. s, 1H, OH), 4.40−4.22 (m, 5H, H-5, H-7a, H-9b, CH_2-1', $J_{7a,7b}$ = 15.6 Hz), 4.21−4.05 (m, 4H, H-2, H-6a, H-6b, H-7b), 2.17−2.06 (m, 5H, CH_2-4', Me, Ac), 2.05 (br. s, 6H, 2 × Me, Ac), 1.97 (s, 3H, Me, Ac), 1.98−1.85 (m, 2H, CH_2-2'), 1.52−1.38 (m, 2H, CH_2-3') ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.8, 170.6, 170.3, 169.3 (3 × *C*O-Ac, *C*O-8), 144.4 (C-10), 137.8 (C-5'), 115.6 (C-6'), 100.0 (C-1), 69.9 (C-3), 68.2 (C-4), 67.7, (C-7), 67.4 (C-5), 66.7 (C-2), 61.8 (C-6), 51.0 (C-1'), 34.7 (C-9), 33.1 (C-4'), 29.3 (C-2'), 25.7 (C-3'), 21.0, 20.8, 20.8 (3 × Me, Ac) ppm. HRMS: calcd. for $C_{23}H_{34}IN_4O_{10}$ [*M* + Na]$^+$ 675.1139, found 675.1140.

{[*N*-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]carbamoyl}methyl 3,4,6-tri-*O*-acetyl-α-D-glucopyranoside (28): CuI/Amberlyst A21-catalysed coupling of (*N*-propargylcarbamoyl)methyl glycoside **4** [18a] (0.115 g, 0.29 mmol) with benzyl azide according to general procedure gave the triazole derivative **28** (92 mg, 60%) as a colorless oil after purification by CC (from EtOAc to EtOAc/methanol, 9:1); R_f = 0.21 (EtOAc). $[\alpha]_D^{20}$ = +64 (c = 0.9, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.24 (br. t, 1H, NH), 7.45 (br. s, 1H, H-11), 7.40−7.33 (m, 3H, Ph), 7.29−7.23 (m, 2H, Ph), 5.47 (s, 2H, CH_2Ph), 5.34 (br. d, 1H, H-3, $J_{2,3}$ = $J_{3,4}$ = 10.0 Hz), 5.02 (t, 1H, H-4, $J_{3,4}$ = $J_{4,5}$), 4.86 (d, 1H, H-1, $J_{1,2}$ = 3.8 Hz), 4.69 (dd, 1H, H-9a, $J_{9a,NH}$ = 7.3, $J_{9a,9b}$ = 15.5 Hz), 4.35−4.19

(m, 3H, H-6a, H-7a, H-9b), 4.09−4.00 (m, 3H, H-5, H-6b, H-7b), 3.84 (dd, 1H, H-2), 2.08 (s, 3H, Me, Ac), 2.06 (s, 3H, Me, Ac), 2.02 (s, 3H, Me, Ac) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 170.8, 169.8, 169.5 (3 × *C*O-Ac, *C*O-8), 145.0 (C-10), 134.2 (Cq, Ph), 129.3, 129.1, 128.3 (*C*H, Ph), 122.1 (C-11), 99.5 (C-1), 72.8 (C-3), 70.3 (C-2), 68.3, 68.2, 67.7 (C-4, C-5, C-7), 62.0 (C-6), 54.5 (C-1'), 34.0 (C-9), 21.0 20.9, 20.8 (3 × Me, Ac) ppm. HRMS: calcd. for $C_{24}H_{30}N_4O_{10}$ $[M + Na]^+$ 557.1860, found 557.1859.

{[*N*-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]carbamoyl}methyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (29) and {[*N*-(1-benzyl-5-iodo-1,2,3-triazol-4-yl)methyl] carbamoyl}methyl 3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (30): CuI/Amberlyst A21-catalysed coupling of (*N*-propargylcarbamoyl)methyl glycoside **8** [18b] (51 mg, 0.13 mmol) with benzyl azide according to general procedure gave the triazole **29** (52 mg, 77 %) as a white solid and its 5-iodo triazole derivative **30** (3 mg, 4%) a a colorless oil after purification by CC (from EtOAc to EtOAc/MeOH, 9:1).

Data for **29**: R_f = 0.24 (EtOAc). m.p. 147–149 ºC. $[\alpha]_D^{20}$ = +2 (c = 0.5, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (t, 1H, NH, J = 5.8), 7.47 (br. s, 1H, H-11), 7.37−7.32 (m, 3H, Ph), 7.26−7.22 (m, 2H, Ph), 5.48 (d, 1H, OH, J = 5.8 Hz), 5.45 (br. s, 2H, C*H*$_2$Ph), 5.14 (d, 1H, H-3, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz), 4.99 (t, 1H, H-4, $J_{3,4}$ = $J_{4,5}$), 4.51−4.37 (m, 3H, H-1, C*H*$_2$-9, $J_{1,2}$ = 7.8, $J_{9a,9b}$ = 15.4 Hz), 4.34 (d, part A of AB system, 1H, H-7a, $J_{7a,7b}$ = 15.6 Hz), 4.25 (dd, part A of ABX system, 1H, H-6a, $J_{5,6a}$ = 4.8, $J_{6a,6b}$ = 12.3 Hz), 4.12 (d, part B of AB system, 1H, H-7b), 4.07 (dd, part B of ABX system, 1H, H-6b, $J_{5,6b}$ = 2.0 Hz), 3.69 (ddd, 1H, H-5), 3.61 (ddd, 1H, 2H), 2.05 (s, 3H, Me, Ac), 2.01 (s, 3H, Me, Ac), 2.00 (s, 3H, Me, Ac) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 170.8, 169.7, 169.6 (3 × *C*O-Ac, *C*O-8), 145.5 (C-10), 134.2 (Cq, Ph), 129.3, 129.0, 128.3 (*C*H, Ph), 122.6 (C-11), 103.1 (C-1), 74.9 (C-3), 72.1 (C-5), 71.8 (C-2), 68.8 (C-7), 68.3 (C-4), 62.0 (C-6), 54.4 (C-1'), 34.1 (C-9), 20.9, 20.8, 20.7 (3 × Me, Ac) ppm. HRMS: calcd. for $C_{24}H_{30}N_4O_{10}$ $[M + Na]^+$ 557.1860, found 557.1861.

Data for **30**: R_f = 0.41 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (br. t, 1H, NH), 7.40−7.32 (m, 3H, Ph), 7.30-7.23 (m, Ph), 5.58 (br. s, 2H, C*H*$_2$Ph), 5.12 (d, 1H, H-3, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz), 5.03 (t, 1H, H-4, $J_{3,4}$ = $J_{4,5}$), 4.61 (dd, part A of ABX system, 1H, H-9a, $J_{9a,NH}$ = 5.5, $J_{9a,9b}$= 15.4 Hz), 4.49−4.35 (m, 3H, H-1, H-9b, H-7a $J_{1,2}$ = 8.1, $J_{7a,7b}$ = 16.1, $J_{9a,9b}$ = 15.4 Hz), 4.29−4.18 (m, 1H, H-6a, H-7b, $J_{5,6a}$ = 4.8, $J_{6a,6b}$ = 12.3 Hz), 4.09 (dd,

part B of ABX system, 1H, H-6b, $J_{5,6b}$ = 2.0 Hz), 3.68 (ddd, 1H, H-5), 3.62 (dd, 1H, 2H), 2.09 (s, 3H, Me, Ac), 2.07 (s, 3H, Me, Ac), 2.03 (s, 3H, Me, Ac) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 170.8, 169.7, 169.4 (3 × *C*O-Ac, *C*O-8), 133.9 (Cq, Ph), 129.1, 128.8, 128.1 (*C*H, Ph), 103.1 (C-1), 75.3 (C-3), 72.3 (C-5), 72.1 (C-2), 68.7 (C-7), 68.1 (C-4), 62.0 (C-6), 54.6 (C-1'), 34.9 (C-9), 21.0, 20.9, 20.8 (3 × Me, Ac) ppm. HRMS: calcd. for $C_{24}H_{29}IN_4O_{10}$ $[M + Na]^+$ 683.0827, found 683.0827.

({*N*-Allyl, *N*-[1-(hex-5-en-1-yl)-1*H*-1,2,3-triazol-4-yl]methyl}carbamoyl)methyl 2,3,4,6-tetra-*O*-allyl-α-D-galactopyranoside (31) and ({*N*-Allyl, *N*-[1-(hex-5-en-1-yl)-1*H*-1,2,3-triazol-4-yl]methyl}carbamoyl)methyl 2,4,6-tri-*O*-allyl-α-D-galactopyranoside (32): To a solution of compound **26** (44 mg, 0.08 mmol) in dry DMF (1.2 mL) was added NaH (0.42 mmol, 60%, 17 mg). After a few minutes, allyl bromide (0.42 mmol, 36 μL) was added and the mixture was stirred at 50 ºC for 1 h. Water was added (8 mL) and the aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic layers were washed with water and dried with Na_2SO_4. After filtration and evaporation of the solvent, the residue was purified by CC (from EtOAc/pentane, 7:3 to EtOAc) to afford **31** (16 mg, 32%) and **32** (9 mg, 20%) as colourless oils.

Data for **31**: R_f = 0.56 (EtOAc/pentane, 7:3). $[\alpha]_D^{20}$ = +19 (c = 1.2, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (s, 1H, H-11), 6.02−5.67 (m, 6H, 5 × C*H* allylic, H-5'), 5.37−5.08 (m, 11H, H-1, 5 × =CH_2 allylic), 5.06−4.93 (m, 2H, =CH_2-6'), 4.60 (d, part A of AB system, H-9a, $J_{9a,9b}$ = 14.9 Hz), 4.53 (d, part A of AB system, H-9b), 4.44−3.83 (m, 16H, 5 × CH_2 allylic, H-2, H-5, CH_2-7, CH_2-1', $J_{1,2}$ = 3.7 Hz), 3.81 (brd, 1H, H-4, $J_{3,4}$ = 3.1), 3.75 (dd, 1H, H-3, $J_{3,4}$ = 2.9, $J_{2,3}$ = 10.1 Hz), 3.62−3.45 (m, 2H, CH_2-6, $J_{5,6a}$ = 6.4, $J_{5,6b}$ = 6.4, $J_{6a,6b}$ = 9.3 Hz), 2.14−2.04 (m, 2H, CH_2-4'), 1.96−1.82 (m, 2H, CH_2-2'), 1.48−1.35 (m, 2H, CH_2-3') ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8 (*C*O-8), 144.2 (C-10), 137.9, 135.5 135.3, 135.3, 134.6, 132.6 (C-5', 5 × *C*H allylic), 123.4 (C-11), 117.5, 117.3, 117.2, 117.0, 116.3 (5 × =*C*H_2 allylic) 115.5 (C-6'), 97.2 (C-1), 78.0 (C-3), 76.0 (C-2), 75.1 (C-4), 74.2 (*C*H_2 allylic-4), 72.5 (*C*H_2 allylic-6), 72.1, 72.1 (*C*H_2 allylic-2, *C*H_2 allylic-3), 70.0 (C-5), 69.0 (C-6), 64.5 (C-7), 50.3 (C-1'), 49.5 (N-*C*H_2 allylic), 41.0 (C-9), 33.1 (C-4'), 29.7 (C-2'), 25.8 (C-3') ppm. HRMS: calcd. for $C_{32}H_{48}N_4O_7$ $[M + Na]^+$ 623.3421, found 623.3423.

Data for **32**: R_f = 0.23 (EtOAc/pentane, 7:3). $[\alpha]_D^{20}$ = +32 (c = 0.7, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (s, 1H, H-11), 6.04-5.58 (m, 5H, 4 × C*H* allylic, H-5'), 5.35−5.11 (m, 9H, H-1, 4 × =CH_2 allylic), 5.07−4.94 (m, 2H, =CH_2-6'), 4.62 (d, part A of AB system, H-9a, $J_{9a,9b}$ = 15.1 Hz), 4.53 (d, part A of AB system, H-9b), 4.40−3.83 (m, 14H, 4 × CH_2 allylic, H-3, H-5, CH_2-7, CH_2-1'), 3.82 (br. d, 1H, H-4, $J_{3,4}$ = 3.1 Hz), 3.73 (dd, 1H, H-2, $J_{1,2}$ = 3.7, $J_{2,3}$ = 10.3 Hz), 3.62−3.50 (m, 2H, CH_2-6, $J_{5,6a}$ = 6.5, $J_{5,6b}$ = 6.5, $J_{6a,6b}$ = 9.3 Hz), 2.17−2.02 (m, 2H, CH_2-4'), 1.99−1.82 (m, 2H, CH_2-2'), 1.52−1.34 (m, 2H, CH_2-3') ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8 (*C*O-8), 144.1 (C-10), 137.9, 135.1, 134.8, 134.5, 132.4 (C-5', 4 × *C*H allylic), 123.4 (C-11), 117.9, 117.6, 117.4, 117.3 (4 × =*C*H_2 allylic) 115.5 (C-6'), 96.1 (C-1), 76.5 (C-4, C-2), 74.5 (*C*H_2 allylic-4), 72.5 (*C*H_2 allylic-6), 71.3 (*C*H_2 allylic-2), 69.9, 69.9 (C-3, C-5), 69.0 (C-6), 64.1 (C-7), 50.4 (C-1'), 49.5 (N-*C*H_2 allylic), 41.0 (C-9), 33.1 (C-4'), 29.7 (C-2'), 25.8 (C-3') ppm. HRMS: calcd. for $C_{29}H_{44}N_4O_7$ [*M* + Na]$^+$ 583.3108, found 583.3105.

{[*N*-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]carbamoyl}methyl 3,6-di-*O*-acetyl-4-deoxy-α-D-*glycero*-hex-3-enopyranosid-2-ulose (33): DMSO/Ac_2O oxidation of compound **28** (88 mg, 0.17 mmol) according to general procedure gave the corresponding 3-enopyranosid-2-ulose **33** (47 mg, 60%) as a colorless oil after purification by CC (from EtOAc/pentane, 4:1 to EtOAc). R_f = 0.40 (EtOAc. $[\alpha]_D^{20}$ = +6 (c = 0.4, in CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.47 (br. s, 1H, H-11), 7.40−7.33 (m, 3H, Ph), 7.29−7.23 (m, 2H, Ph), 7.04 (br. t, 1H, NH), 6.64 (d, 1H, H-4, $J_{4,5}$ = 1.7 Hz), 5.49 (br. s, 2H, CH_2Ph), 5.02 (s, 1H, H-1), 4.95 (td, 1H, H-5), 4.57−4.51 (m, 2H, CH_2-9) 4.41 (dd, part A of ABX system, 1H, H-6a, $J_{5,6a}$ = 5.3, $J_{6a,6b}$ = 11.7 Hz), 4.31 (d, part A of AB system, 1H, H-7a, $J_{7a,7b}$ = 15.1 Hz), 4.25−4.14 (m, 2H, H-6b, H-7b, $J_{5,6b}$ = 4.5 Hz), 2.25 (s, 3H, Me, Ac), 2.10 (s, 3H, Me, Ac) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.6 (*C*O), 170.7, 168.1, 167.9 (2 × *C*O-Ac, *C*O-8), 141.8 (C-4), 134.6 (Cq, Ph), 133.2 (C-3), 129.2, 128.9, 128.2 (*C*H, Ph), 98.1 (C-1), 68.4, 68.3 (C-5, C-7), 64.3 (C-6), 54.3 (C-1'), 34.7 (C-9), 20.8, 20.4 (2 × Me, Ac) ppm. HRMS: calcd. for $C_{22}H_{24}N_4O_8$ [*M* + Na]$^+$ 495.1492, found 495.1493.

{[*N*-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]carbamoyl}methyl 3,6-di-*O*-acetyl-2,4-dideoxy-2-*C*-[(*E*)-(ethoxycarbonyl)methylene]-α-D-*glycero*-hex-3-enopyranoside (34): CuI/Amberlyst A21-catalysed coupling of (*N*-propargylcarbamoyl)methyl

glycoside **22** (20 mg, 0.05 mmol) with benzyl azide according to general procedure gave the triazole derivative **34** (23 mg, 87%) as a white solid after purification by CC (from EtOAc/pentane, 7:3 to EtOAc). R_f = 0.43 (EtOAc). m.p. 172–174 ºC. $[\alpha]_D^{20}$ = +10 (c = 0.2, in CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57 (br. t, 1H, NH), 7.48 (s, 1H, H-11), 7.39−7.32 (m, 3H, Ph), 7.29−7.23 (m, 2H, Ph), 6.36 (s, 1H, H-1), 5.93 (dd, 1H, H-4, $J_{2',4}$ = 0.8, $J_{4,5}$ = 2.0 Hz), 5.89 (br. d, 1H, H-2'), 5.48 (s, 2H, CH_2Ph), 4.69 (ddd, 1H, H-5), 4.60 (dd, part A of ABX system, 1H, H-9a, $J_{9a,NH}$ = 6.3, $J_{9a,9b}$= 15.4 Hz), 4.50 (dd, part B of ABX system, 1H, H-9b, $J_{9a,NH}$ = 6.0 Hz), 4.37−4.27 (m, 2H, H-6a, H-7a, $J_{5,6a}$ = 5.8, $J_{6a,6b}$ = 11.6, $J_{7a,7b}$ = 15.6 Hz), 4.24 (d, part B of AB system, 1H, H-7b), 4.18−4.09 (m, 3H, H-6b, CH_2CH$_3$, $J_{5,6b}$ = 4.0, J = 7.1 Hz), 2.26 (s, 3H, Me, Ac-3), 2.09 (s, 3H, Me, Ac-6), 1.25 (t, 1H, CH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 169.2, 168.0 (2 × *C*O-Ac, *C*O-8), 165.4 (*C*O), 145.4 (C-10), 142.0, 140.1 (C-2, C-3), 134.7 (Cq, Ph), 129.3, 128.9, 128.2 (*C*H, Ph), 122.5 (C-11), 121.3 (C-4), 114.4 (C-2'), 94.3 (C-1), 67.1, 66.8 (C-5, C-7), 68.7 (C-7), 64.9 (C-6), 61.3 (*C*H_2CH$_3$), 54.3 (C-1'), 34.7 (C-9), 21.0, 20.9 (2 × Me, Ac), 14.3 (*C*H_2CH$_3$) ppm. HRMS: calcd. for $C_{26}H_{30}N_4O_9$ $[M + Na]^+$ 565.1910, found 565.1914.

General Procedure for Deacetylation of Compounds 25, 26, 28 and 29: A solution of 2,3,4,6-tetra-*O*-acetylated glycoside (0.03 mmol) in $CH_3OH/H_2O/NEt_3$ (8/1/1, 2 mL) was stirred overnight at 40 ºC. After evaporation of the solvents under vaccum, the residue was purified by CC.

{[*N*-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]carbamoyl}methyl-α-D-galactopyranoside (35): Deacetylation ($CH_3OH/H_2O/NEt_3$) of glycoside **25** (19 mg, 0.036 mmol), according to general procedure afforded compound **35** (12 mg, 82%) as a colorless oil after purification by CC (EtOAc/MeOH, 4:1). R_f = 0.23 (EtOAc/methanol, 4:1). $[\alpha]_D^{20}$ = +61 (c = 1, in MeOH/CH_2Cl_2, 1:1). ^{1}H NMR (400 MHz, MeOD): δ = 7.87 (br. s, 1H, H-11), 7.42−7.28 (m, 3H, Ph), 5.57 (s, 2H, CH_2Ph), 4.85 (d, 1H, H-1, $J_{1,2}$ = 3.5 Hz), 4.51 (s, 2H, CH_2-9), 4.21 (d, part A of AB system, H-7a, $J_{7a,7b}$ = 15.9 Hz), 4.03 (d, part B of AB system, H-7b), 3.88 (br. d, 1H, H-4, $J_{3,4}$ = 3.3 Hz), 3.84−3.63 (m, 5H, H-2, H-3, H-5, H-6a, H-6b, $J_{2,3}$ = 10.3, $J_{5,6b}$ = 5.0, $J_{6a,6b}$ = 11.3 Hz) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 172.3 (*C*O-8), 136.7 (Cq, Ph), 130.0, 129.6, 129.2 (*C*H, Ph), 124.3 (C-11), 101.2 (C-1), 73.1 (C-3), 71.3 (C-5), 71.0 (C-4), 70.0 (C-2), 67.9 (C-7), 62.8 (C-

6), 55.0 (C-1'), 35.2 (C-9) ppm. HRMS: calcd. for $C_{18}H_{24}N_4O_7$ $[M + Na]^+$ 431.1543, found 431.1544.

({*N*-[1-(Hex-5-en-1-yl)-1*H*-1,2,3-triazol-4-yl]methyl}carbamoyl)methyl-α-D-galactopyranoside (36): Deacetylation ($CH_3OH/H_2O/NEt_3$) of glycoside **26** (17 mg, 0.032 mmol), according to general procedure afforded compound **36** (12 mg, 95%) as a colorless oil after purification by CC (EtOAc/MeOH, 4:1). $[\alpha]_D^{20}$ = +33 (c = 0.6, in $MeOH/CH_2Cl_2$, 1:1). R_f = 0.32 (EtOAc/methanol, 5:1). ^{1}H NMR (400 MHz, MeOD): δ = 7.88 (br. s, 1H, H-11), 5.88−5.71 (m, 1H, H-5'), 5.07−4.91 (m, 2H, H-6'a, H-6'b), 4.86 (d, 1H, H-1), 4.52 (s, 2H, CH_2-9), 4.39 (t, 2H, CH_2-1'), 4.24 (d, part A of AB system, H-7a, $J_{7a,7b}$ = 15.5 Hz), 4.05 (d, part B of AB system, H-7b), 3.89 (br. d, 1H, H-4, $J_{3,4}$ = 3.1, $J_{4,5}$ = 1.0 Hz), 3.85−3.64 (m, 5H, H-2, H-3, H-5, H-6a, H-6b, $J_{1,2}$ = 3.1, $J_{2,3}$ = 10.1, $J_{5,6b}$ = 5.3, $J_{6a,6b}$ = 11.1 Hz), 2.14−2.06 (m, 5H, CH_2-4'), 1.98−1.84 (m, 2H, CH_2-2'), 1.46−1.35 (m, 2H, CH_2-3') ppm. ^{13}C NMR (100 MHz, MeOD): δ = 172.3 (*C*O-8), 146.0 (C-10), 139.2 (C-5'), 124.2 (C-11), 115.5 (C-6'), 101.3 (C-1), 73.1 (C-3), 71.3 (C-5), 71.0 (C-4), 70.0 (C-2), 68.0 (C-7), 62.8 (C-6), 51.2 (C-1'), 35.2 (C-9), 34.1 (C-4'), 30.7 (C-2'), 26.8 (C-3') ppm. HRMS: calcd. for $C_{17}H_{28}N_4O_7$ $[M + Na]^+$ 423.1856, found 423.1858.

{[*N*-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]carbamoyl}methyl-α-D-glucopyranoside (37): Deacetylation ($CH_3OH/H_2O/NEt_3$) of glycoside **28** (17 mg, 0.032 mmol), according to general procedure afforded compound **37** (12 mg, 92%) as a colorless oil after purification by CC (EtOAc/MeOH, 4:1). R_f = 0.24 (EtOAc/methanol, 4:1). $[\alpha]_D^{20}$ = +57 (c = 1.1, in $MeOH/CH_2Cl_2$, 1:1). ^{1}H NMR (400 MHz, MeOD): δ = 7.88 (br. s, 1H, H-11), 7.41−7.29 (m, 3H, Ph), 5.57 (s, 2H, CH_2Ph), 4.81 (d, 1H, H-1, $J_{1,2}$ = 3.8 Hz), 4.51 (s, 2H, CH_2-9), 4.22 (d, part A of AB system, H-7a, $J_{7a,7b}$ = 15.6 Hz), 4.03 (d, part B of AB system, H-7b), 3.80 (dd, part A of ABX system, H-6a, $J_{5,6a}$ = 2.2, $J_{6a,6b}$ = 11.8 Hz), 3.68−3.61 (m, 2H, H-3, H-6b), 3.54 (ddd, 1H, H-5, $J_{4,5}$ = 9.8, $J_{5,6b}$ = 5.8 Hz), 3.43 (dd, 1H, H-2, $J_{2,3}$ = 9.6 Hz), 3.33 (dd, 1H, H-4, $J_{3,4}$ = 9.1 Hz) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 172.2 (*C*O-8), 146.3 (C-10), 136.7 (Cq, Ph), 130.0, 129.6, 129.2 (*C*H, Ph), 124.3 (C-11), 101.0 (C-1), 74.9 (C-3), 74.4 (C-5), 73.3 (C-2), 71.6 (C-4), 67.8 (C-7), 62.5 (C-6), 55.0 (C-1'), 35.2 (C-9) ppm. HRMS: calcd. for $C_{18}H_{24}N_4O_7$ $[M + Na]^+$ 431.1543, found 431.1541.

{[*N*-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methyl]carbamoyl}methyl-β-D-glucopyranoside (38): Deacetylation ($CH_3OH/H_2O/NEt_3$) of glycoside **29** (16 mg, 0.03 mmol), according to general procedure afforded compound **38** (11 mg, 90%) as a white solid after purification by CC (EtOAc/MeOH, 4:1). R_f = 0.24 (EtOAc/methanol, 4:1). m.p. 154–155 ºC. $[\alpha]_D^{20}$ = –11 (c 0.8, in MeOH/CH_2Cl_2, 1:1). ^{1}H NMR (400 MHz, MeOD): δ = 7.87 (br. s, 1H, H-11), 7.41−7.29 (m, 5H, Ph), 5.57 (s, 2H, C*H*$_2$Ph), 4.53 (d, part A of AB system, H-9a, $J_{7a,7b}$ = 15.4 Hz), 4.48 (d, part B of AB system, H-9b), 4.35−4.28 (m, 2H, H-1, H-7a, $J_{1,2}$ = 7.8, $J_{7a,7b}$ = 15.9 Hz), 4.17 (d, part B of AB system, H-7b), 3.83 (dd, part A of ABX system, H-6a, $J_{5,6a}$ = 1.8, $J_{6a,6b}$ = 12.1 Hz), 3.65 (dd, part A of ABX system, H-6b, $J_{5,6b}$ = 5.3 Hz) 3.89−3.21 (m, 4H, H-2, H-3, H-4, H-5) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 172.4 (*C*O-8), 136.7 (Cq, Ph), 130.0, 129.6, 129.2 (*C*H, Ph), 124.3 (C-11), 104.7 (C-1), 78.2 (C-5), 77.8 (C-3), 74.9 (C-2), 71.4 (C-4), 69.5 (C-7), 62.5 (C-6), 55.0 (C-1'), 35.2 (C-9) ppm. HRMS: calcd. for $C_{18}H_{24}N_4O_7$ [*M* + Na]$^+$ 431.1543, found 431.1543.

2. Biological evaluation

2.1. Antimicrobial Activity

The antibacterial and antifungal activity of compounds **13**–**15**, **18**, **21**–**24** and **25**−**26**, **28**−**29**, **31**–**38** was evaluated using the paper disk diffusion method according to the standard procedure CLSI (Clinical Laboratory Standards Institute/National Committee for Clinical Laboratory Standards) [36]. The following bacteria and fungi were used in the tests: *Enterococcus faecalis* (ATCC 7080), *Escherichia coli* (ATCC 25922), *Listeria monocytogenes* (ATCC 19115), *Salmonella enteritidis* (ATCC 13076), *Staphylococcus aureus* (ATCC 6538), *Bacillus cereus* (ATCC 11778), *Bacillus subtillis* (ATCC 6633), *Aspergillus niger* (ATCC 16404) *Botrytis cinerea* (ESAS), *Candida albicans* (ATCC 10231), *Penicillium aurantiogriseum* (ATCC 16025). The overnight cultures of the microorganisms were spread over the appropriate media, nutrient agar for all bacteria except *Listeria*, where triptone soya agar was used. Potato dextrose agar was used for fungi. Paper disks of 6.4 mm were placed on the agar and a solution of each substance (300 μg) in DMSO (15 μL) was applied on each disk. Chloramphenicol (for *Bacillus cereus*, *Bacillus subtillis*, *Enterococcus faecalis*, *Escherichia coli*, *Listeria*

monocytogenes, *Salmonella enteritidis*, *Staphylococcus aureus*) and actidione and amphotericine B (for *Aspergillus niger*, *Botrytis cinerea*, *Candida albicans*, *Penicillium aurantiogriseum*) were used as positive controls and DMSO was used as negative control. Bacteria were incubated at 37 ºC for 24 h and fungi at 25 ºC for 24 h to 48 h. After incubation, the plates presented a biomass lawn and, when applicable, the nearest diameter of the inhibition zones formed was measured. Results were the average of two replicates.

The antimicrobial activity was classified according to the diameter of inhibition zones (∅), as follows: very strong activity, ∅≥26 mm, +++++; strong activity, 22 mm≤∅<26 mm, ++++; good activity, 18 mm≤∅<22 mm, +++; moderate activity, 14 mm≤∅<18 mm, ++; weak activity, 12 mm≤∅<14 mm, +; no activity, ∅<12mm, –.

2.2. Acute Toxicity

Acute cytotoxicity measurements were performed by the MTT method [38]. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was used to quantify metabolically viable cells in all samples. Adherent cells (mouse HII4E hepatoma cells) were seeded onto 96-well plates, allowed to attach for 24 h and exposed to the test compound for the following 24 h. Positive control (hydrogen peroxide) and negative control (DMSO) were also included. At 48 h of culture MTT was added to the cells at a final concentration of 0.5 mg/mL, followed by an incubation period of 3 h to allow the formazan crystals to form. After incubation, medium was removed, cells were washed twice to remove traces of medium and un-metabolized MTT, and DMSO (100 μL) was added to each well. Solubilization of formazan crystals was performed by agitation in a 96-well plate shaker for 20 min at room temperature. Absorbance of each well was quantified at 550 nm using 620 nm as reference wavelength on a scanning multiwall spectrophotometer (automated plate reader).

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3. General Conclusions

Bicyclic carbohydrate lactones were explored as targets and as precursors for the inclusion of α,β-unsaturated carbonyl systems in sugar backbones.

Butenolide-containg sugars were prepared in few steps by intramolecular cyclization approaches, based on the Wittig reaction of furanos-3-uloses or furanos-5-uloses with a resonance stabilized ylide and lactonization of intermediate γ-hydroxyl α,β-unsaturated esters.

For the synthesis of butenolides C-C-linked to a furanose moiety, the configuration at C-3 was an important structural feature which controlled the stereochemistry of the Wittig product and consequently the lactonization. Only *ribo*-furanos-5-ulose derivatives gave the target butenolides, while *xylo*-5-uloses did not allow the formation of the suitable stereoisomers for spontaneous cyclization.

Protected furanos-3-uloses were converted in 2-4 steps into bicyclic pento- or hexopyranose-based systems comprising a butenolide moiety fused to positions 2,3 or to positions 3,4 of the sugar ring. Their Wittig olefination to the corresponding furanose-3-*C*-branched α,β-unsaturated esters was followed by acid hydrolysis, which elicited both intramolecular lactonization and furanose to pyranose ring expansion.

The scope of this method was widened to thiosugar analogues and new highly functionalized and potential biologically interesting bicyclic thiosugar derivatives were generated.

When applying a similar approach to related furanoid 5-amino α,β-unsaturated ester precursors, aiming at the synthesis of imino sugar-fused butenolides, a different outcome for the 5-aminofuranose/iminopyranose isomerization was observed and it was shown to be dependent of the pH. The target bicyclic butenolide could not be isolated after deprotection of the (*Z*)-δ-amino α,β-unsaturated ester, instead it underwent rearrangement in basic medium to a butenolide-containing *N*-ethylformamide derivative. In neutral conditions, dehydration of the iminoalditol occurred, which was followed by tautomerization to a 2-keto imino sugar. The latter, upon acetylation, furnished a 1,2-dihydropyridin-3-one. This is an innovative and facile method to obtain this class of compounds, which synthesis is reported in the literature in low global yield.

This molecule is structurally suitable to be a useful synthon for new imino sugar derivatives. Enones of this family have been used as key intermediates for the synthesis of natural products including glycosidase inhibitors such as 1-deoxynojirimycin, deoxymannojirimycin and deoxygulonojirimycin.

In contrast to the (*Z*)-δ-amino α,β-unsaturated ester, its (*E*)-isomer suffers a pontaneous intramolecular cyclization to afford a bicyclic α,β-unsaturated δ-lactam in very good yield.

These new nitrogen-containing sugar derivatives constitute interesting synthons for derivatization and novel candidates for bioactivity expression.

The Wittig olefination-intramolecular cyclization method thus allowed to get a variety of carbohydrate derivatives, including *S*- or *NH*- analogues, comprising moieties which make them structurally suitable for derivatization and for evaluation of their biological activity, in few and simple steps and good overall yields.

Bicyclic lactones derived from carboxymethyl glycosides proved to be useful synthons for the acquisition of pyranoid systems comprising conjugated carbonyl functions, such as 3-enopyranosid-2-uloses and pyranoid 2-*C*-branched-chain conjugated diene esters.

The ability of these lactones to be readily opened by amines was the key aspect of the synthetic methodology implemented since the release of a free hydroxyl group at C-2 allowed further derivatization at this position. Hence, oxidation of the resulting tri-*O*-acetyl glycopyranosides occurred with concomitant elimination to afford the target enones. The yields obtained were far better for α-enulosides than for the β-anomers, due to their higher conformational stability. The α-enones were converted in pyranoid conjugated diene esters by Wittig reaction. Glycosides bearing *N*-propargyl moieties were coupled with a terminal azide in the presence of a heterogeneous CuI/Amberlyst catalytic system to give the corresponding 1,2,3-triazoles in good yields.

The biological evaluation performed in some of the newly synthesized compounds revealed significant activities for the monocyclic pyranoid systems. The low

antibacterial and antifungal effects observed for the bicyclic derivatives comprising a butenolide moiety reflect their poor Michael acceptor ability.

3-Enopyranosid-2-uloses containing a (*N*-dodecylcarbamoyl)methyl aglycon moiety exhibited strong and very strong activities against some of the pathogens tested. The α-enuloside showed very strong effect towards two *Bacillus* species, namely *Bacillus subtillis* and the pathogenic *Bacillus cereus*, which is is commonly involved in food-borne diseases and is recognized as a causative agent in both gastrointestinal and in nongastrointestinal infections. The inhibition diameters observed were equal or even higher as those of chloramphenicol, the control used for the bacteria tested. Its inhibitory effect against the fungal pathogen *Penicillium aurantiogriseum* also surpassed that of the control actidione. The β-anomer displayed very strong activity against the fungi *Penicillium aurantiogriseum and Aspergillus niger* with inhibition diameters similar or higher than those obtained for the standard antibiotic. The latter fungus is recognized to cause plant infections, such as black mold on certain fruits and vegetables and is a common contaminant of food. Its pathogenicity in humans includes the lung disease aspergillosis, common in horticultural workers, and ear infections (otomycosis). *P. aurantiogriseum* has been described as responsible for blue mold decay in storage apple fruits. It is a producer of a number of mycotoxins, whose health effects were not reported yet.

These bioassays suggest that the hydrophobic portion of the enulosides must play a key role in the bioactivity, since enones possessing propargyl and benzyl moieties were virtually ineffective.

Enterococcus faecalis is one of the most common bacteria involved in a variety of serious infections amongst hospitalised patients, including urinary tract infections, wound infections, peritonitis or endocarditis. This microbe was susceptible to the dodecyl-containing α-enuloside and to the pyranoid conjugated diene esters and a strong effect was observed.

None of the triazole derivatives showed significant antimicrobial effect.

Among the bioactive compounds, three showed low acute toxicity values, including the α-(*N*-dodecylcarbamoyl)methyl enuloside. The strong activity observed for the latter compound, associated with low toxicity, motivates the investigation of its mechanism of action. The promising results obtained also encourage further studies on the effect of the relevant bioactive molecules towards other biological targets. Synthesis of lead series based on their structure to evaluate their potency, in particular against these pathogenic microbes, and to minimize toxicity will also be required for application as therapeutic agents against the affected pathogens.

In summary, in the present work, highly functionalized carbohydrate derivatives comprising an α,β-unsaturated carbonyl function were synthesized by new, simple and efficient approaches. The presence of the conjugated carbonyl functionality rends them suitable bioactive candidates and potential scaffolds for derivatization. In particular, new leads against clinically significant pathogens were generated.

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